MEDICAL PROCEEDINGS

MEDIESE BYDRAES

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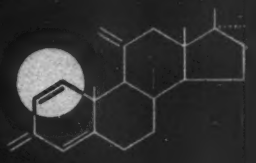

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REDAKSIONEEL

INENTING TEEN POLIOMIËLITIS

Nadat die Francis-verslag van 12 April 1955 verklaar het dat die entstof wat sonder enige onheil vir die Salk se reusagtige veldproefneming met sowat 2 miljoen kinders gebruik is, ‚veilig, doeltreffend en kragtig' is, is daar 'n begin gemaak met die grootskeepse inenting van 'n vermoedelik vatbare bevolking. Ná 27 April het dit geblyk dat sekere kinders wat ingeënt is met 2 van die 9 hoeveelhede entstof wat deur die Cutter-laboratoriums vervaardig en vrygestel is, verlamming in die ingeënte ledemaat ontwikkel het. Teen 24 Mei was daar 59 gevalle van paralitiese poliomiëlitis onder die 409,000 kinders wat met die Cutter-entstof ingeënt is, en die aanvalsyfer was 7 keer hoër as wat verwag is. Die hele Amerikaanse program het gevolglik tot stilstand gekom, en die posisie is in heroorweging geneem.

Die dramatiese kansellering van die voorgestelde proefneming met 'n poliomiëlitis-bestrydingsentstof van 'n Salk-tipe in Groot-Brittanje, soos aangekondig deur dr. G. S. Wilson namens die Britse Mediese Navorsingsraad, en die ewe dramatiese besluit om die posisie in Suid-Afrika in heroorweging te neem, het ernstige besorgheid en verwarring onder sowel geneeshere as leke tot gevolg gehad. Die Britse beswaar is gegrond op die moeilikhede verbonde aan die vernietiging van die lewensvatbaarheid (maar nie die vermoë om teenstowwe te vorm nie) van die entstof wat met formaldehide voorberei word, en 'n verklaring deur so 'n vooraanstaande gesaghebbende soos dr. Wilson moet noodwendig swaar weeg.

Tog is dit moontlik dat die onvoorwaardelike veroordeling van die Amerikaanse proefneming té ingrypend is. Daar is die welslae wat met die

EDITORIAL

VACCINATION AGAINST POLIOMYELITIS

After the Francis report of 12 April 1955 had evaluated the vaccine used without a single catastrophe in the vast field trial conducted by Dr. Salk on some 2 million children as 'safe, effective, potent', mass vaccination of the presumably susceptible population was begun. From 27 April onwards it appeared that certain children receiving vaccine from 2 lots out of 9 manufactured and released by the Cutter Laboratories, were developing paralysis in the injected limb. By 24 May there were 59 cases of paralytic poliomyelitis among 409,000 children vaccinated with the Cutter vaccine, an attack rate 7 times higher than was to be expected. The whole American programme ground to a standstill and the position came under review.

The dramatic cancellation of the proposed trial of a Salk-type anti-poliomyelitis vaccine in Great Britain, announced by Dr. G. S. Wilson on behalf of the British Medical Research Council, and the equally dramatic decision to bring the position under review in South Africa, caused grave concern and confusion among doctors as well as laymen. The British objection was based on the difficulty of destroying the viability (but not the antigenicity) of the vaccine prepared with formaldehyde, and a statement from such an authority as Dr. Wilson must carry considerable weight.

Yet the unqualified indictment of the American experiment may nevertheless have been too sweeping. There was the success of the initial field trial. There is the further fact (reported by Surgeon General Leonard A. Scheele to the American Medical Association) that among 5,200,000 children who got vaccine

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aanvanklike proefneming behaal is. Daar is die verdere feit (soos aangemeld deur Geneesheer-generaal Leonard A. Scheele by die Amerikaanse Mediese Vereniging) dat onder die 5,200,000 kinders wat met entstof uit ander bronne as die Cutter-laboratoriums behandel is, die gevalle van poliomiëlitis nie die ‚perke wat van toevallige gebeurlikhede verwag kan word' oorskry het nie. Van groot betekenis is ook die feit dat geen enkele geval van paralitiese poliomiëlitis voorgekom het na die gebruik van die vernietigde entstof wat deur Parke, Davis & Kie, voorberei is nie, hoewel 834,000 kinders met hierdie entstof behandel is. Ook die Pitman-Moore-entstof het onberispelike resultate opgelewer. Onder die 2,500,000 kinders wat ingeënt is met die entstof voorberei deur Eli Lilly & Kie, het daar 11 gevalle van verlamming voorgekom. Die waarde van hierdie syfer kan egter nie bepaal word tensy dit vergelyk word met die aantal gevalle van paralitiese poliomiëlitis onder kinders in dieselfde gebied wat nie ingeënt is nie. Sulke gegewens is nie beskikbaar nie. Die Wyeth-entstof is geassosieer met 5 gevalle van verlamming wat nie aan die entstof toegeskryf word nie. Hierdie feite bewys onteenseglik dat dit moontlik is om met formaldehide 'n vernietigde entstof voor te berei wat volkome veilig is. Dis derhalwe duidelik dat veel van individuele tegniese vernuf by die voorbereiding van die entstof afhang, en dit skyn asof daar geen regverdiging is nie vir die algehele veroordeling van alle vorms van vernietigde entstof as onveilig, wanneer daar getuienis is dat etlike miljoene kinders volkome veilige inentings gekry het. *Die mate waarin hulle teen poliomiëlitis beskerm is, is 'n saak wat op latere ontleding wag.*

Ten gevolge van die talle nuwe variabiliteite wat geïntroduseer word, bring die grootskeepse produksie van 'n vernietigde entstof probleme mee wat hulle nie voordoen as die vervaardigingsproses op 'n laboratorium-skaal geskied nie. Ervare kennis is dus van die allergrootste belang, soos sommige van die vooraanstaande Amerikaanse farmaseutiese firmas reeds bewys het. In Kanada is die probleem op 'n effens ander manier aangepak. Die Mediese Navorsingslaboratoriums Connaught (Universiteit van Toronto) het sommige van die moeilikhede verbonde aan grootskeepse produksie omseil deur die entstof in kleiner hoeveelhede te vervaardig. Kinders het onderhuidsinspuitings gekry, nie binnespierse inspuitings nie. Trouens, teen die einde van Junie is ongeveer 900,000 kinders ingeënt sonder dat daar 'n enkele geval van verlamming wat aan die toe-

from other sources than the Cutter Laboratories, the cases of poliomyelitis were 'within the range expected by chance occurrence'. Very significant also is the fact that not a single case of paralytic poliomyelitis developed after the use of the killed vaccine prepared by Parke, Davis & Co., although this vaccine was used on 834,000 children. The Pitman-Moore vaccine also had a spotless record. In 2,500,000 children inoculated with the vaccine prepared by Eli Lilly and Company, 11 cases of paralysis occurred. This figure cannot be evaluated unless it is compared with the number of cases of paralytic poliomyelitis among uninoculated children in the same area. These data are not available. The Wyeth vaccine was associated with 5 cases of paralysis not attributed to the vaccine. These facts prove conclusively that it is possible to make a killed vaccine with formaldehyde which is utterly safe. Clearly, therefore, much depends on individual technical skill in the preparation of the vaccine and there seems no justification for a wholesale condemnation of all forms of killed vaccine as unsafe when there is evidence that several million children have had completely safe inoculations. *The extent to which they have been protected against poliomyelitis is a matter which awaits analysis in due course.*

Mass production of a killed vaccine creates problems which do not arise when the manufacture is carried out on a laboratory scale, because of the new variables introduced. Thus the 'know-how' becomes all important, as some of the leading American pharmaceutical houses have proved. In Canada the problem was dealt with in a slightly different way. The Connaught Medical Research Laboratories (University of Toronto) avoided some of the difficulties of mass production by manufacturing the vaccine in smaller amounts. Children were injected subcutaneously and not intramuscularly. Indeed, by the end of June some 900,000 children had been inoculated without a single case of paralysis resulting from the vaccine administered, thus once again proving that it is reasonably practicable to produce a safe killed vaccine.

The problem of manufacturing a vaccine may be complicated by the fact that different strains of the same type of virus vary in their virulence. It is also not unreasonable to infer from this that different strains of the same type might well vary in their ability to be killed by formaldehyde. The margin between safety (i.e. destruction of viability) and antigenicity (i.e. the power to evoke immune bodies) is small. Thus there may be other

gediende entstof toegeskryf kon word, voorgekom het. Weereens is daar dus bewys dat dit redelik moontlik is om 'n veilige vernietigde entstof te produseer.

Die probleem verbonde aan die vervaardiging van 'n entstof kan ingewikkelder gemaak word deur die feit dat daar 'n verskil is in die giftigheid van verskillende soorte virusse van dieselfde tipe. Met die oog hierop is dit nie onredelik nie om te veronderstel dat die weerstandskragtigheid van verskillende soorte virusse van dieselfde tipe teen die vernietigende uitwerking van formaldehide waarskynlik ook verskil. Die grens tussen veiligheid (d.w.s. die vernietiging van lewensvatbaarheid) en antigenisiteit (d.w.s. die vermoë om teenstowwe te vorm) is klein. Gevolglik is dit moontlik dat daar ook ander vrugbare navorsingsgebiede is. Die soektog na 'n soort virus met 'n geringe mate van giftigheid of glad geen giftigheid nie (maar wat nogtans sy vermoë behou om teenstowwe te vorm) kan bes moontlik 'n virusstof oplewer wat geskik is òf vir die voorbereiding van 'n vernietigde entstof, òf (soos Koprowski aangetoon het) van 'n lewende entstof wat veilig per mond toegedien kan word en langdurige ontvatbaarheid tot gevolg het. Daar is die teoretiese verwagting dat waneer ontvatbaarheid per mond verwerf word, dit miskien lewenslank sal duur. Per slot van rekening, dit is, sover ons weet, die manier waarop die infeksie op 'n natuurlike wyse opgedoen, en blywende onvatbaarheid verkry word. Veel kan waarskynlik aangevoer word vir 'n nabotsing van die natuur op hierdie manier. Maar dis duidelik dat alle pogings om die elemente van gevaar uit te skakel sonder haas moet geskied, en dat sulke pogings teen openbare lawaaierigheid en emosionalisme beskerm moet word.

Dit beteken natuurlik nie dat 'n vernietigde entstof die antwoord op die probleem van onvatbaarmaking teen poliomiëlitis is nie. Dit skyn nie asof die natuur in alle gevalle 'n eentonig eenselwige patroon volg nie. 'n Vernietigde entstof is bv. volkome doeltreffend as voorbehoedmiddel teen tifoïde-infeksies, terwyl toksoïde die probleem van witseerkeel opgelos het. Daarenteen het 'n lewende virus van verswakte giftigheid 'n oplossing in die geval van pokkies en geelkoors gebied, maar 'n verswakte organisme (in die vorm van BCG-entstof) het beslis nie daarin geslaag om die mediese wetenskap te oortuig dat dit 'n veilige of doeltreffende middel vir die voorkoming van tuberkulose is nie. Dit kan gebeur dat die soektog na 'n verswakte vorm van die poliomiëlitisvirus 'n veilige basis vir inenting teen hierdie

fruitful lines of investigation. The search for strains of low virulence or without virulence (which retain their antigenicity) may well provide virus material suitable either for the preparation of a killed vaccine or (as Koprowski has shown) for a live vaccine which could safely be taken by mouth with the production of prolonged immunity. There is a theoretical expectation that when immunity is acquired by mouth, it may be life-long. After all, as far as we know, this is the way in which the infection is acquired naturally with permanent immunity. There may be much to be said for imitating Nature in this way. But clearly all attempts to eliminate the elements of danger should be unhurried and protected from public clamour or emotionalism.

It does not, of course, follow that a killed vaccine is the answer to the problem of immunization against poliomyelitis. Nature does not seem to follow a monotonously identical pattern in each case, e.g. a killed vaccine is completely effective prophylactically against the typhoid infections, whereas toxoid solved the diphtheria problem. On the other hand a living virus of attenuated virulence has given the solution in the case of smallpox and of yellow fever, but an attenuated organism (in the form of BCG vaccine) has been strikingly unsuccessful in convincing medical science of its safety or efficacy in preventing tuberculosis. It may be that the search for an attenuated form of the poliomyelitis virus will provide a safe basis for vaccination against this infection; and in the light of present knowledge this is an avenue which must clearly be explored very vigorously. We cannot, however, be certain that it will give the complete answer.

The decision of the British Medical Research Council clearly indicates the need for a careful re-appraisal of the situation in South Africa. If there is general agreement that the only adequately sensitive test-object for the virus is the human child, we should seriously reconsider whether we are in a good enough position to release a killed vaccine mass produced in the Union, as it has been decided to do (according to the Minister's statement of 27 July 1955). The South African vaccine, according to the Minister in the *Rand Daily Mail* of 28 July 1955, differs in material respects from the Salk vaccine as it contains a higher concentration of the agent rendering it harmless and does not contain the virulent strain responsible for the recent accidents in the U.S.A. These differences may affect the efficacy of the vaccine considerably and al-

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infeksie sal verskaf; en in die lig van ons huidige kennis is dit 'n gebied wat sorgvuldig ondersoek sal moet word. Maar ons kan nie met sekerheid verklaar dat dit die volledige antwoord sal oplewer nie.

Die besluit van die Britse Mediese Navorsingsraad dui sonder enige twyfel aan dat die posisie in Suid-Afrika hersien sal moet word. As daar algemeen ingestem word dat die enigste doeltreffend gevoelige toets-voorwerp vir die virus 'n kind is, sal ons ernstig moet heroorweeg of ons in 'n sterk genoeg posisie verkeer om 'n vernietigde entstof wat massagewyse in die Unie geproduseer is, beskikbaar te stel, soos daar besluit is om te doen (volgens die Minister se verklaring van 27 Julie 1955). Die Suid-Afrikaanse entstof, volgens die Minister in die *Rand Daily Mail* van 28 Julie 1955, verskil in materiële opsigte van die Salkentstof, aangesien dit 'n hoër konsentrasie bevat van die agens wat dit onskadelik maak, en nie die giftige soort bevat wat verantwoordelik vir die onlangse ongelukke in die Verenigde State van Amerika was nie. Hierdie verskille kan 'n aansienlike effek op die doeltreffendheid van die entstof uitoefen, en hoewel die Minister se raadgewers meen dat ons entstof veilig is, slaan hulle die waarde daarvan nie hoër aan as ‚waarskynlik doeltreffend' nie. In die *Rand Daily Mail* van 29 Julie het dr. Nelson, mediese gesondheidsbeampte, Pretoria, gewaarsku dat die doeltreffendheid van die entstof onbekend is. 'n Ondoeltreffende entstof kan 'n ongeoorloofde en miskien gevaarlike gevoel van veiligheid by sowel diegene wat ingeënt is as by die publiek in die algemeen laat ontstaan, en aanleiding gee tot die onnodige uitgawe van reusagtige bedrae geld.

Die Britse Mediese Navorsingsraad het tot 'n ander gevolgtrekking geraak op grond van dieselfde getuienis wat tot ons beskikking is, maar die Minister se raadgewers is blykbaar nie bereid om die Britse voorbeeld aan te beveel nie. Aangesien die plaaslike entstof in werklikheid 'n ander soort entstof is, behoort ons op die allerminste die versigtige prosedure te volg wat in die Verenigde State toegepas is voordat daar tot die grootskeepse inenting van die bevolking oorgegaan word. Ons behoort, met ander woorde, 'n doeltreffend (en statisties) beheerde voorlopige proefneming met 'n voldoende aantal vrywilligers te doen.

Die gevaar van poliomiëlitis word in baie kringe veels te hoog aangeslaan. Min kan gewen, en veel kan bes moontlik verloor word deur oorhaastige optrede. Veel kan gesê word ten gunste daarvan dat die voorbereiding van 'n vernietigde, veilige, kragtige entstof oorgethough the Minister's advisers think that our vaccine is safe they do not rate its value as more than 'probably efficacious'. In the *Rand Daily Mail* of 29 July, Dr. Nelson (M.O.H., Pretoria) warned that the effectiveness of the vaccine was an unknown quantity. An ineffective vaccine may create an unwarranted and possibly dangerous sense of security in the inoculated as well as in the population generally, and lead to the unnecessary expenditure of vast sums of money.

The British Medical Research Council came to a different conclusion on the same evidence available to us, but the Minister's advisers are apparently not prepared to recommend the British example. As the local vaccine is in effect a different vaccine, at the very least we should follow the careful procedure which was adopted in the U.S.A. before mass inoculation of the population was begun, viz. the carrying out of an adequately (and statistically) controlled pilot experiment on a sufficient number of volunteers.

The menace of poliomyelitis has been greatly overrated in many quarters. There is little to be gained (and possibly much to be lost) by precipitate action. There is a lot to be said for leaving the preparation of a killed, safe, potent vaccine to those already experienced in this field and to await the development of such a vaccine in the U.S.A. after its protective value has been assessed in the current poliomyelitis season in that country. It would seem more sensible (and probably cheaper) to buy our requirements (when a completely safe vaccine has been devised) from organizations which have the facilities, the time and the opportunity to deal with such a problem.

If our own resources were no longer focused on the mass production of a killed vaccine (i.e. on what is virtually a commercial enterprise) a considerable body of highly skilled man power in the Union would be released for concentrated research on fundamental problems in virology.

The course of conduct which the Medical Research Council in the United Kingdom has embarked on is undoubtedly also an excellent way in which we in the Union could contribute to the universal pool of scientific knowledge. The experience which the Americans have already gained in producing a safe and potent killed vaccine is something we cannot hope to match in this country. We would be better advised to direct our combined scientific energies into relatively unexplored channels which may yet yield fundamental contributions to the solution of this grave problem.

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laat moet word aan diegene wat reeds ondervinding op hierdie gebied opgedoen het, en om te wag op die ontwikkeling van so 'n entstof in die Verenigde State, nadat die beskermde waarde daarvan tydens die huidige poliomiëlitisseisoen in daardie land behoorlik vasgestel is. Miskien sal dit raadsamer (en waarskynlik ook goedkoper) wees om ons benodigdhede te koop (nadat 'n volkome veilige entstof ontwikkel is) van organisasies wat oor die fasiliteite, die tyd en die geleentheid beskik om so 'n probleem die hoof te bied.

As ons eie hulpbronne nie langer toegespits is op die grootskeepse produksie van 'n vernietigde entstof, d.w.s. op wat feitlik 'n handelsonderneming is nie, kan heelwat hoogs ervare arbeidskragte in die Unie vrygestel word vir gekonsentreerde navorsing na die fundamentele probleme van die virologie.

Die stappe wat deur die Mediese Navorsingsraad in die Verenigde Koninkryk gedoen word, is sonder die minste twyfel ook 'n voortreflike manier vir ons hier in die Unie om 'n bydrae tot die wetenskaplike kennis van die wêreld te lewer. Die ondervinding wat die Amerikaners opgedoen het vir sover dit die produksie van 'n veilige en kragtige vernietigde entstof betref, is iets wat ons in hierdie land nie kan hoop om te ewenaar nie. Vir ons is dit derhalwe gerade om ons gesamentlike wetenskaplike energie toe te spits op betreklik onbekende kanale wat miskien nog fundamentele bydraes tot die oplossing van hierdie ernstige probleem kan lewer.

THE WISDOM OF HIPPOCRATES

Life is short, science is long; opportunity is elusive, experiment is dangerous, judgment is difficult. It is not enough for the physician to do what is necessary, but the patient and the attendants must do their part as well, and circumstances must be favourable.

* * *

In the case of athletes too good a condition of health is treacherous if it be an extreme state; for it cannot quietly stay as it is, and therefore, since it cannot change for the better, can only change for the worse. For this reason it is well to lose no time in putting an end to such a good condition of health, so that the body can start again to reconstitute itself. Do not allow the body to attain extreme thinness for that too is treacherous, but bring it only to a condition which will naturally continue unchanged, whatever that may be. Likewise fasting, if taken to extremes, is treacherous; and so also is putting on weight, if excessive.

* * *

Desperate cases need the most desperate remedies.

* * *

In acute diseases employ drugs very seldom and only at the beginning. Even then, never prescribe them until you have made a thorough examination of the patient.

* * *

When a disease has attained the crisis, or when a crisis has just passed, do not disturb the patient with innovation in treatment either by the administration of drugs or by giving stimulants. Let them be.

* * *

Use drugs only when the disease for which you employ them has come to a head and not when it is developing, unless it be ripe for such treatment, which is rarely the case.

(From *The Medical Works of Hippocrates*, translated by J. Chadwick and W. N. Mann. Oxford: Blackwell Scientific Publications.)

NOTES AND NEWS · BERIGTE

Dr. J. K. Bremer, M.B., Ch.B., F.R.C.S. (Eng.), het op 1 Julie 1955 verhuis na Van Riebeek Mediese Gebou 409, Schoemanstraat 295, Pretoria, waar hy sy chirurgiese praktyk sal voortsit. (Telefone—*Spreekkamers*, 2-7741; *Woning*, 4-2802.

* * *

Dr. Charles Sarkin, M.B., B.Ch. (Rand), F.R.C.S. (Edin.), has commenced practice as an orthopaedic surgeon at 67 Jenner Chambers, Jeppe Street, Johannesburg. (Telephones—*Rooms*, 23-2003; *Residence*, 41-1750.)

* * *

Dr. Louis Hirsowitz, M.D., has commenced practice as a Physician at 204 Medical Centre, Jeppe Street, Johannesburg. (*Telephones*—Consulting Rooms: 23-0742; Residence: 40-2975.)

* * *

Dr. Carlos D. Guerrero, General Secretary of the International Fertility Association, Melchor Ocampo 487-202, Mexico 5, D.F. Mexico, announces that Dr. Werner Weinberg of Johannesburg has been elected Associate Editor for Abstracts in South Africa of the new international journal *Fertility*.

Dr. M. M. Suzman has recently returned from a 2-month trip to the United States and Great Britain.

In the U.S.A. he was invited to participate in a *Conference on Nutrition in Infections* sponsored by the New York Academy of Science. The Chairman of the Conference was Dr. W. A. Wright, Medical Director of Pfizer Laboratories.

He also attended the First International Conference on the *Clinical and Metabolic Effects of Meticorten and Meticortelone* in New York, sponsored by the Clinical Research Division of the Schering Corporation, Bloomfield, New Jersey. At Atlantic City he participated in the 37th Annual Meeting of the Endocrine Society. He was present at the Annual Meeting of the International Society of Angiology, and of the Society of Vascular Surgeons as well as the Annual Convention of the American Medical Association.

Dr. Suzman lectured on Nutrition to the Bureau of Nutrition of the Department of Health of the City of New York, at the invitation of its Director, Dr. Norman H. Jolliffe.

He acted as Visiting Chief of Medical Service *pro tempore* at the Massachusetts General Hospital, Boston, for 2 weeks at the invitation of Dr. Walter Bauer.

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AETIOLOGY OF INFANTILE INTUSSUSCEPTION

WILFRED KARK, F.R.C.S.

Department of Surgery, University of the Witwatersrand, Johanneburg

Numerous theories have been offered to explain the aetiology of intussusception in infants, but many aspects of the subject are not yet clarified. This paper, based upon a review of 37 cases dealt with over the past 5 years, is offered as a contribution to these debatable issues.

In a series of 702 patients, Gross[1] records that in about 6% of cases in infants a definite lesion, in the shape of an intra-luminal projection or mass, could be demonstrated as the starting point of the intussusception, but that the 'etiologic factor in 90 to 95% of childhood intussusceptions is still unknown'.

In this regard there is a striking dissimilarity between intussusception in infants and in older ages. During later childhood, adolescence and adult life, a distinct aetiogenic agent, most commonly in the form of a tumour or Meckel's diverticulum, is manifest in the great majority of cases. This conspicuous and remarkable difference has been the mainspring of a number of the older theories of causation and it has also provided the main stimulus to the present investigation.

Apart from the element of an intra-luminal mass there is a second major factor in the production of intussusception, viz. abnormal peristaltic activity. That it plays a part is generally accepted, but whether it is invariably a secondary phenomenon, i.e. as a reaction to a mass within the lumen of the bowel, or whether abnormal peristalsis could also be a primary and initiating factor is an aetiological problem of interest and importance.

The place of these two aetiological agents, viz. intra-luminal mass and disturbances of peristalsis, provide the substance of this paper.

ABNORMAL PERISTALSIS

The history preceding the advent of the intussusception was analysed to discover whether there was any upset of normal peristaltic activity. The findings may be listed under the following heads:

Gastro-Enteritis. In 5 of the 37 cases the intussusception was preceded by a gastro-enteritis associated with diarrhoea and vomiting. In conformity with other reports, intussusception in this series also occurred mostly as a sudden and dramatic event in an otherwise healthy and fit child without any prodromal symptoms or clinically recognizable precipitating features.

Laxatives. In 3 cases a laxative had been administered within 3 days before the intussusception. In none of these cases was there any evidence of colic or diarrhoea following the administration of the laxative.

Allergy. The possibility of hyperperistalsis as an allergic reaction is difficult to elicit in the histories of these infants. In the present series there was no case in which there was

TABLE I

	Bottle-fed from Early Days of Life	*Breast-fed at Time of Intussusception*	*After Weaning Had Begun*
Total Number	6	8	23
Cases with Special Features	In 2 cases, more solid mixtures had been introduced into the diet within 1 week of the intussusception. In 1 case, fruit juice had been added within one week of the intussusception. Two cases occurred after 1 year of age. No change in diet.	Within one week of the intussusception: In 2 cases, a night feed had been stopped. In 1 case, orange juice had been added. Two cases had gastro-enteritis.	Fourteen cases had some change, in the form of supplementary or complementary feeds, within 2 weeks of the onset of intussusception. Of the 14 cases, 2 had gastro-enteritis. Of the other 9 cases, 1 had gastro-enteritis.

any reasonable suggestion to incriminate allergy, either in the family history or in the infant's personal background.

Sex. Twenty-six of the 37 cases occurred in boys.

Age. Twenty-nine cases occurred between the fourth and tenth months of life.

Diet. Tables I and II analyse the findings.

TABLE II: TIME OF ONSET OF INTUSSUSCEPTION IN RELATION TO COMMENCEMENT OF WEANING

Time After Weaning	*Number of Cases*
Within 2 weeks	5
Within 4 weeks	4
Within 8 weeks	2
Within 3 months	6
Within 4 months	2
Within 6 months	2
More than 9 months later ..	2

The analysis of the 23 cases in Table II (giving the time of onset of the intussusception in relation to the commencement of weaning, viz. the first supplementation of a breast feed) does not appear to be of much consequence; but the findings in respect of changes in the diet after weaning (as indicated in Table I) appear to carry more significance.

A finding of importance not recorded in the Tables is an impression that in healthy male infants who have gained weight rapidly, weaning tends to be started at an earlier age, and progress to solid foods is more rapid.

INTRA-LUMINAL MASS

An attempt was made at operation to assess the precise site of the apex of the intussusceptum, mainly by observation of the ultimate portion of intussuscepted bowel to be reduced. This was aided by the evidence of the site of maximum oedema in the reduced bowel.

During the course of these observations, it became clear that there were isolated instances when the apex of the intussusceptum altered during reduction, and that it was not therefore solely at the neck, i.e. the junction of the returning and ensheathing layers, that the change in length of the intussusceptum occurred. This appears to upset the dictum by Souttar[2] who wrote: 'The growth of an intussusception occurs exclusively at the neck. The apex of the intussusception soon becomes oedematous, stiff and swollen, and once this has happened it is impossible for the apex to change'. This also imposes a reservation upon the current observations in that the final segment of bowel reduced in the course of an operation is not invariably the apex of the intussusceptum.

TABLE III: SITE OF APEX (MAXIMUM OEDEMA)

Group 1. Ileo-caecal valve	16
Group 2. Caput caeci	13
Group 3. Ileum	5
Group 4. Base of Appendix	3

There was but little doubt about the *first group* in which the ileo-caecal valve was judged to be the apex and starting point of the intussusception. The valve was palpably and unmistakably enlarged and after its reduction there was no further residual invagination of the bowel. In a number of cases, hot towels were applied to the region of the valve in an attempt to reduce the secondary oedema, but restitution to anything approaching a normal size was not achieved in any single instance.

In one case, in addition to the enlarged ileo-caecal valve, an additional oedematous area was also found on the caput caeci; in no other case in the series was there more than one site of oedematous swelling.

In the *second group* (caput caeci), the ultimate point of reduction of the intussusceptum was not so definite as in the first group. It could not be visualized unequivocally; and it was only after final reduction, which was usually achieved with facility and in which the caecum, the ileo-caecal valve and terminal ileum all seemed to reduce together, that a patch of maximum oedema was found on the anterior surface of the caecum. The patch was situated between ½–1 inch lateral to, and a similar distance higher than the base of the appendix; it measured an average of about ½ inch in diameter; it was a clearly definable entity involving the whole thickness of the wall of the caecum, and on palpation between the fingers it gave the impression of forming a projection into the lumen of the caecum. It could quite readily be invaginated into the caecum and upwards into the ascending colon by light digital pressure, and it appeared to be the probable starting point.

In this second group the size of the ileo-caecal valve was not found to be abnormally large: the exception already referred to was included in the group of ileo-caecal cases.

In the *third group* (where the apex of the intussusceptum was found to be in the ileum)

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one case was due to a Meckel's diverticulum, 2 were due to adenomatous tumours, and in the remaining 2 a definite lesion was not discovered. In 3 cases in this group resection of a portion of the bowel was required because of the presence of irreversible strangulating changes. It was in 2 of these resections that the adenomata were found. The third resection did not reveal any lesion.

In the 3 cases (*group* 4) labelled as oedema of the base of the appendix, the swelling also involved the adjacent area of the caecum and constituted a distinct entity in which the appendicular base was set eccentrically. Again, in this group the ileo-caecal valve was of normal proportion and there was no other site of oedema.

DISCUSSION

In addition to the reservation already noted about the few instances in which there was apparent change in the position of the apex, there is another important consideration which might invalidate some of the deductions made from the recorded findings. This is the possibility that the palpable swelling found after the completion of reduction is wholly an oedema which arises as a phenomenon secondary to the growing intussusception. The error may occur when the oedema is in the apex itself or at some site other than the apex. Theoretically this is particularly possible in the group of cases where the maximum oedema was found in the caput of the caecum. In the course of the development and growth of an intussusception arising in the ileo-caecal region from some site other than the caecal caput, the advancing lesion will often implicate the mesentery of the terminal ileum and also the vessels of the caecum. It may be argued that this vascular compromise is responsible for the oedematous patch on the caput caeci, for the location of this oedematous patch is situated in that area of the caecum furthest away from the stems of the ileo-caecal vessels. It is at this same place in the bowel wall that viability is first threatened in cases where an obstruction of large bowel advances to a closed-loop type with severe intracolonic pressure effects.

If this feature were common, it might reasonably be expected that 2 distinct sites of oedema would often be found, one referable to the apex of the intussusception and the other due to the secondary vascular compromise arising from the growth of the intussusception. However, in this series, 2 such sites of oedema were found in only one case; there was oedema of the ileo-caecal valve in addition to oedema of the caput caeci. This particular case has been classified in the ileo-caecal group because the ileo-caecal valve was the last portion of the intussusception to be reduced.

If the swelling of the apex of the intussesceptum is a secondary phenomenon, it follows that it cannot dogmatically be held that any swelling existed before the invagination of the portion of bowel concerned. However, the association of the swelling and the ultimate point of reduction can reasonably be held to be of significance in determining the seat of origin of the intussusception and in the evaluation of the possible causes of the condition.

With these reservations in mind, the findings can be interpreted as indicating that in many (and perhaps in most) cases there is a strong probability that some intra-luminal projection is the starting point of intussusception. As a concept of the aetiology this has been the basic assumption underlying the theories of Walton,[3] Perrin and Lindsay[4] and Brenner.[5] These theories included the hypothesis that it was an enlargement of lymph follicles or Peyer's patches that had formed the tumour. But such theorizing offers no explanation for the difference in the incidence in the sexes, nor does it square with the investigations of Boyd,[6] who found that lymphoid tissue reaches its maximum relative size during the pre-puberty years when the incidence of intussusception is very low.

The higher incidence in males and in healthy, muscular subjects is of some moment in relation to the tumefaction as the starting point of invagination. The suggestion is that the sphincters of the bowel share in the enlargement of the more powerful musculature of such infants, and the enlarged ileo-caecal valve, perhaps because of its special position (as suggested by Boyd[7]) at the junction of small and large bowel where there is such a disparity in relative sizes, is apt to become the equivalent of a foreign body which, by peristalsis, is driven onwards into the caecum and colon.

In the cases in the second group, in which the swelling was found in the caput caeci, the possibility of some intra-luminal projection can readily be visualized. It seems likely that such a projection consists of a large mucous or haustral fold. Such a suggestion is supported by the cases reported by Grasso[8] and Sovena.[9] Certainly the feel of the oedematous patch with the sense of substance in the

wall of the caecum suggests tumefaction at this site as the starting point of the intussusception. This possibility will be more fully developed in the discussion on peristaltic activity.

In the group where the base of the appendix was judged to be the apex of the intussusception, there was similarly a distinct impression of a projection of swollen tissue into the caecum.

In the third group characterized by an initial ileo-ileal intussusception with subsequent advance into the colon, there is clear evidence in 3 of the 5 cases of an intra-enteric lesion acting as the starting point of the invagination.

That excessive and abnormal peristalsis, whether electrically or pharmacologically stimulated, is a cause of intussusception has been shown experimentally by Nothnagel,[10] who produced the condition by faradic stimulation, and by Propping[11] who used physostigmine. Fitzwilliams[12] and Matti[13] were among the first to suggest that in infants the frequent occurrence of ileo-caecal intussusception was due to irregular and uncontrolled peristalsis. Those cases in which invagination occurs in the course of a gastro-enteritis offer further evidence that abnormal peristalsis is a possible causative agent.

It is widely held that the high proportion of cases occurring in the 4–10 month age group is indicative of weaning or change of diet as the exciting cause of abnormal peristalsis and therefore of intussusception. Moreover, the stronger and more muscular the infant, the more vigorous will be the peristaltic activity, and so the greater incidence in boys and in healthy muscular subjects finds a ready explanation. In the present series, the relative incidence in the age groups and in healthy male children conformed to that generally described. The occurrence in this series of cases with earlier weaning and more rapid advance to solid foods in healthy male infants also supports the view that dietary change is an aetiological factor.

The other factors influencing peristalsis (as analysed in Table I and more particularly in Table II) are equivocal. In some of the groups there are suggestive pointers relating intussusception to causes of altered peristaltic rhythm, but there is no definite or constant correlation and therefore only limited inferences are warranted. It is quite possible that some features bearing upon the question of peristaltic activity were completely missed in the histories of the cases. This is an aspect that further experience may clarify.

There appears to be a close and mutually reciprocal relation between abnormal peristalsis and the factor of a projection into the bowel lumen. A foreign body (or a mass acting as a foreign body) within the bowel is the normal stimulus to peristaltic activity, with the result that the foreign body is moved onwards. The more resistance this foreign body offers (seen especially in an extreme form when it causes an obstruction) the more powerful is the reacting peristaltic activity. On the other hand, excessive or abnormal peristalsis may be stimulated by other factors, e.g. inflammatory enteritis. In such circumstances a segment of bowel may undergo spastic contraction which persists for a relatively long period, during which active peristaltic rhythm more proximally may drive the contracted portion as if it were a foreign body into the distal part and so initiate an invagination. In the light of the support provided by radiological evidence in spastic conditions of the bowel, it is readily conceivable that hyperperistalsis and excessive segmental contraction, particularly in large bowel, can give rise to an exaggeration of the mucous and haustral folds and throw them into such prominence as to create temporarily an intraluminal mass which may, by peristalsis, become the starting point of an intussusception.

SUMMARY

There is an appreciable body of evidence, both comparative and actual, that the prime aetiogenic factor giving rise to the formation of intussusception in infants is the presence of a projection into the lumen of the bowel. Such a projection or mass behaves as a foreign body and most frequently consists of an enlarged ileo-caecal valve.

Another, almost equally common site for the initiation of invagination is an area in the anterior wall of the caecum. It is possible that this site consists of an enlarged mucous or haustral fold, brought into exaggerated prominence by abnormal peristalsis.

Less frequently the intra-luminal mass is situated in the terminal portion of the ileum, and make take the form of inflammatory tumefaction, neoplasm or a Meckel's diverticulum. More uncommonly still, the base of the appendix, enlarged, e.g. by inflammatory irritation or by swelling of its lymphatic tissues, may form the node which excites an invagination of the bowel.

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OPSOMMING

Heelwat getuienis—sowel vergelykend as werklik—kan aangevoer word om te bewys dat die vernaamste aetiogeniese faktor wat aanleiding tot die vorming van intussussepsie of derminstulping gee, die aanwesigheid van 'n projeksie in die buisholte van die derm is. So 'n projeksie of massa tree as 'n vreemde voorwerp op, en bestaan meestal uit 'n vergrootte ileosekale klep.

'n Ander en byna ewe gewone plek vir die aanvang van instulping of invaginasie is die streek in die voorste wand van die blindederm. Moontlik bestaan hierdie streek uit 'n vergrootte slym- of haustra-vou waaraan uitermatige prominensie verleen is ten gevolge van abnormale dermbewegings.

Minder dikwels is die intra-luminale massa geleë in die onderste gedeelte van die dunderm, waar dit die vorm van 'n ontstekingsgeswel, neoplasme of 'n uitstulping van Meckel kan aanneem. Nog seldsamer is die gevalle waar die basis van die blindederm wat vergroot is, bv. ten gevolge van ontstekingsprikkeling of deur 'n swelsel van sy limfweefsels, die knoop kan vorm wat op invaginasie van die derm uitloop.

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THE SCOPE OF RADIATION THERAPY

INCLUDING RADIO-ACTIVE ISOTOPES

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(*Continued from p.* 33)

SIEVE OR GRID X-RAY THERAPY

As one of the main limiting factors to X-ray therapy is the effect on the skin, it was appreciated early on that if the skin could be protected to some extent, larger doses and consequently greater effects in depth would be attained. Adequate doses would thus be given to the tumours in depth. Kohler (quoted by Jolles[1]) protected the skin as early as 1909 by dividing up the treatment area into portions, some of which were covered by a metal screen (similar to the wire net used over windows) while others were open to the radiation beam. Kohler demonstrated in 1912 that the dose regarded as maximum under the conditions of treatment at that time could be increased five-fold in this way.

No practical use was made of this knowledge until 1933, when the perforated sieve was re-introduced in the U.S.A. by Liverson, who used various sizes of sieve perforations. Jolles mentions attempts also made about the same time in Germany by Haring to reproduce the distribution of radiation, obtained from interstitial radium, by the use of a fine sieve with apertures only 3 mm. in diameter. He was able to give about 350% of the usual skin erythema dose without causing necrosis of the skin.

Other workers on the Continent continued these experiments with various types of grid, but again there was no practical application until the subject was revived by Jolles[1] in England and later by Marks[2-4] and by Freid, Lipman and Jacobson[5] and by Harris[6, 7] in the U.S.A. By September 1951 Harris had completed the treatment of 127 patients with this

method. Jolles, however, treated mainly accessible tumours (and a large proportion of skin tumours), whereas the American workers treated deep-seated, inoperable and incurable tumours.

Although Jolles claims results in such superficial tumours as epitheliomata of the skin, these tumours do not lend themselves for comparison with other methods of treatment because they are radio-sensitive and readily curable by most techniques, whether by X-ray with varying voltages, superficial or deep, or by radium, superficial or implantation.

The Americans point out that a statistical study is not feasible with their cases because they sought mainly palliative treatment in hopeless cases. In individual cases this object was obtained because the palliation was greater than could have been expected with routine X-ray methods. All Harris' cases were hopeless from the point of view of surgery or conventional radiotherapy. The primary object of treatment was the relief of pain, haemorrhage and other symptoms. Most of his patients had had previous surgery or standard radiotherapy.

The type of grid and the technique adopted by Jolles differs in some respects from that of the American workers.

Jolles prefers a lead grid (1-3 mm. thick), mounted on aluminium or perspex to absorb secondary radiation. His grid openings are 1-1.5 cm. square and the ratio of the open to the closed portions is 40%.

After 50% or more of the dose has been delivered in some cases, Jolles alters the position of the grid and treats through the reciprocal portion, i.e. the areas formerly protected are now treated whereas the previously treated areas are now protected.

In the U.S.A., on the other hand, lead rubber (4-5 mm. thick, depending on the kilovoltage used) is preferred for the grid material (Figs. A, B). The thicker grids are used with higher kilovoltages, e.g. 400 K.V.

The lead-rubber grid only allows from 1-3% of the incident beam to reach the skin under the covered portions. It also absorbs the secondary radiation and there is no need for a secondary filter. We, too, have found the lead-rubber grid easier to handle. The apertures in both types of grid vary from 1-1.5 cm. wide. The larger grids are more useful in areas such as the axilla. The American authors quoted do not use the reciprocal portion of the grid, preferring to keep it in the same position throughout the treatment.

The doses administered through the grid were at first far higher in the U.S.A. than those used by Jolles. Whereas Jolles gives up to 10,000 r through the grid, Marks was at first giving as much as 24,000 r through the grid. With these heavy doses a number of cases of radio-necrosis was obtained. These heavy doses were criticized in the U.S.A. by Lenz and Failla, and Harris himself. The doses in the U.S.A. have now been cut to 10,000-15,000 r units. The individual doses vary from 500-1,200 r per sitting and the overall period of treament is 28 days, extended in some cases by Harris to 45 days. Jolles does not exceed a total dose of about 10,000 r and also gives as much as 500 r at a sitting. We, ourselves, start

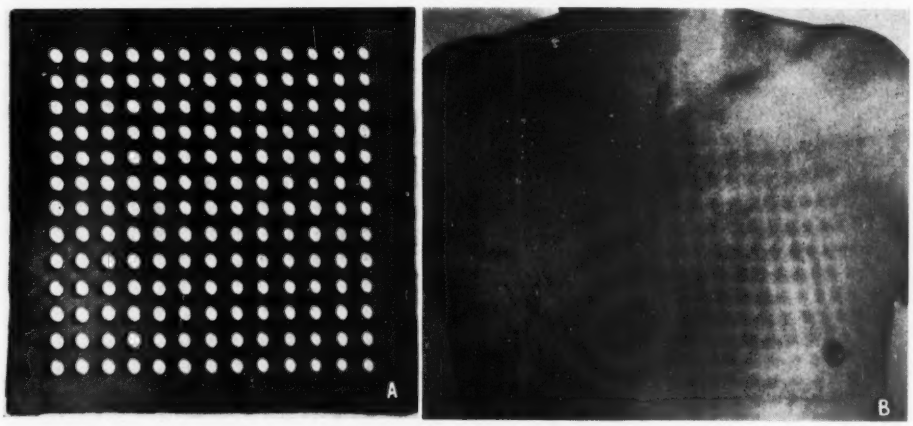

Fig. A. A 0.5 cm. thick lead rubber grid. The holes are 1 cm. in diameter.
Fig. B. The medial area received 9,900 r. The lateral area received 6,000 r.

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with a lower dosage preferring to build up to 500 r over a period of days while watching the reaction of the patient. We do not exceed a total of 10,000-12,000 r, seldom going to the higher figure. Like Harris, we use multiple fields according to the depth of the lesion.

Grid treatment gives reactions similar to those obtained with the standard radiotherapy, local and general. Care must be taken in treating areas which have previously been treated with routine X-ray therapy. It is absolutely essential in grid treatment that every area should be set up by a radiotherapist at every session, so that the same areas of skin are always protected. Treatment should not be left to be applied by a technician by means of a formula.

The heavy doses administered through the open ports of the grid may lead to a moist reaction on the skin, but the healing of the affected areas is facilitated by the alternating adjacent protected areas.

Jolles[1] and Loevinger[8] have shown by biopsy and by measurements that although the skin itself is protected by the closed portions of the grid, there is a considerable amount of radiation in the tissues under the closed ports. According to the tables published by Freid *et al.*, the amount of radiation steadily increases under the protected portions in depth from about 1-7 cm. where it reaches a maximum. There is thus an improvement in depth dose under the closed ports.

Freid *et al.* claim that the tolerance dose of the skin with a grid through the open ports is as much as 27,500 r and under the closed ports is 5,150 r at the surface. Under the closed ports at 10 cm. the tolerance dose is 3,770 r and under the open portions it is 6,300 r. Without a grid for the same area and the same conditions of treatment the depth dose under these conditions at 10 cm. is only 1,620 r units and the surface dose without a grid is only 4,500 r units.

With increase in the depth dose under the closed portions of the grid the radiation becomes more uniform in depth. It has actually been claimed that it is possible with the grid to give about 3 times the depth dose obtained under similar conditions without a grid.

To account for the fact that the unhomogeneity of the radiation decreases in depth, i.e. there is some effect from the radiation under the protected parts of the grid, Jolles postulates that there is a diffusible substance in irradiated tissues which spreads to the neighbouring protected tissues and that this accounts for the reactions seen on biopsy under the protected areas of the sieve. He also demonstrated that the effect of one dose on 2 areas close to each other is greater than if the 2 areas are separated by a definite minimum distance (depending on the size of the areas concerned). For instance, for an area of 2.43 sq. cm. the range of reaction of the diffusible substances in irradiated tissues is 2 cm. For an area of 6.25 sq. cm. the range is given by Jolles as 3 cm. He also points out that the beams of direct radiation through the open ports show a steady falling off in intensity in depth, while the radiation under the protected areas increases to a maximum and then gradually diminishes, the radiation in depth becoming more uniform and the grid pattern tending to be lost in depth (depending on the physical factors used in the radiation). Loevinger has confirmed this.

Another advantage of the grid method claimed by Jolles is that the tumour bed and the stroma, quite apart from the skin, are also protected under the closed portions of the grid. As the stroma and the tumour bed play an important part in recovery from radiation as well as in the effect on the tumour, the grid method has advantages over standard X-ray therapy.

Failla considers that if a dose as high as 24,000 r is given through the open ports, the protected area will get as much as 3,300 r and therefore the reaction of the shielded portions of the skin will be the same as under routine deep X-ray therapy. He therefore advises with Lenz that the dose should be reduced. Failla also considers it an advantage of grid therapy that recovery should take place more easily in the mass of tissue when small heavily irradiated regions are surrounded by regions that have been less heavily irradiated. He maintains that this also applies to the tumour and therefore attempts should be made to overlap the beams in the tumour, while there is less overlapping in the intervening tissues between the skin and the tumour.

Failla also claims that as the radiation becomes fairly uniformly distributed at a depth of 10 cm. there is no point in irradiating more superficial tissues, e.g. malignant glands in the neck. There seems no great point in using a grid on a condition say less than 5 cm. deep, although Jolles has done so on superficial skin tumours.

We have confined the grid technique mainly to lung cancers and mediastinal tumours of the Hodgkin type. It has already been indicated that until a large number of cases has been

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treated it will not be possible to give any comparative statistics of the various methods of treatment, particularly as in our cases we felt obliged to make use of all the methods recently suggested to sensitize tumours to radiation, e.g. oxygen inhalation before and during the treatment and Synkavit injection.

Theoretically, on a physical basis, there are obvious advantages in the grid treatment as it improves the depth doses which can be administered. Del Regatto has referred to this method as the poor man's substitute for supervoltage radiation and rotation therapy.

The cost of supervoltage apparatus is enormous and there are great difficulties in estimating the dosage delivered with rotation therapy. Consequently there are dangers with these methods of treatment. Grid therapy, however, does not mean an increase in the cost of apparatus as the grid only costs a few shillings and the daily observation of the skin supplies a safety factor and prevents overdosage. Moreover, multiple ports can be used with the grid under routine therapy, limiting the dosage to 10,000 r to each grid area.

The disadvantage of the grid is that it prolongs the treatment time and consequently the expense of running the apparatus. It is far less expensive, however, than supervoltage therapy which can only be provided by the wealthy institutions with all the facilities of an elaborate physics department.

RADIUM, RADON AND RADIO-ACTIVE COBALT

Other means of delivering ionizing radiations are from radium, its disintergration product radon and the radio-active isotopes. Radium was discovered at very much the same time as X-rays, and the possibility of its therapeutic use was soon investigated.

Radium may be used in various ways, e.g. by external application through what we have regarded until recently as very large sources of up to 10 gm. bombs or radium beam therapy.

The enormous expense of radium and the complicated apparatus necessary to protect personnel and patient made the development of the radium bomb a slow process. The 1 gm. bomb (at one time considered large) would cost £7,000–£8,000 for the radium alone, without the pneumatic appliances developed to handle the radium.

There are only about 6 of the 10 gm. bombs in operation in Great Britain and fewer than this in the U.S.A. There is one 50 gm. bomb under the control of Professor Maisin in Belgium. Even the 10 gm. bomb is not a large source of radiation, and cannot be used at long distances from the patient in the same manner as an X-ray tube. The radium bomb has to be brought down to distances of 8–10 cm. or less and is mainly used for the treatment of tumours around the neck. The objections to the radium bomb are its vast expense and the limitation of the percentage depth dose because the apparatus has to be brought close to the patient.

The introduction of the radio-active cobalt bomb (which may go up to 2,000 curies and thus be equivalent to about 3,000 gm. of radium, i.e. ±300 times the largest radium bomb used in Great Britain) has brought home the inadequacy of the radium bomb, in view of its vast expense. Cobalt bomb treatment can be given at the same distances from the patient and so gives the same relative percentage depth dose as the deep X-ray therapy tube. Provision of these vast quantities of radio-active material, e.g. 2,000 curies of radio-active cobalt, creates a great problem in the protection of the patient and the personnel. (The radio-active cobalt bomb will be dealt with in a later section on radio-active isotopes).

For small and superficial lesions radium in the form of applicators made up of radium sources in tubes are used for therapy. A tumour of the skin can be treated in this way or an epithelioma of the lip can be cross-fired by a saddle-shaped applicator containing radium on the inside and the outside of the lip.

Radium is frequently the best method of treatment under certain conditions when it is used in needles of various lengths and in different strengths. In carcinoma of the anterior two-thirds of the tongue, radium implant in the form of needles is the treatment generally selected. In a carcinoma of the bladder, radium implantation or (for more superficial conditions), radon, the disintegration product of radium, is frequently used. Radium needles are very useful in the treatment of thick cancers of the skin.

In all the examples quoted the gamma component of the radium rays has been used for treatment because the heavy filters (ranging from 5 mm. of platinum upwards) filter out the beta and the alpha rays. Radium, however, can also be used so that the beta component plays the main part. These sources are put up in the form of radium plaques with light monel metal filters for the treatment of superficial skin conditions, and have also been used for the treatment of benign and malignant eye conditions.

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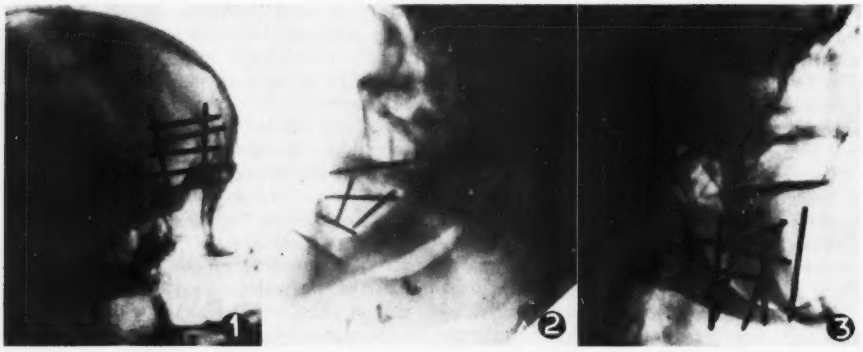
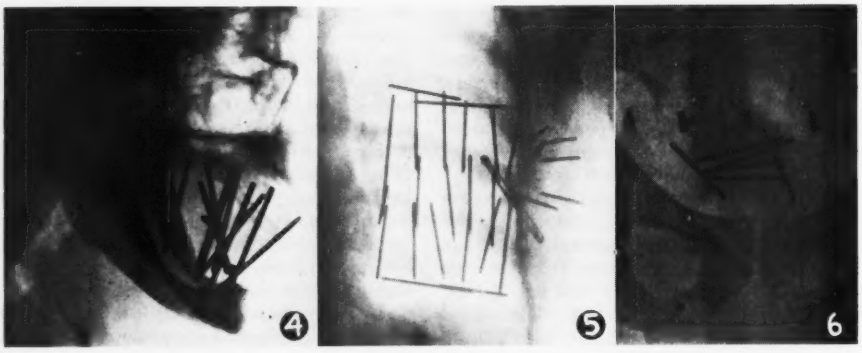




Various methods of application are illustrated in Figs. 1–17.

Single plane radium implant for a large rodent ulcer on the right temple (Fig. 1).

Single plane radium implant for a squamous epithelioma of the inner side of the right cheek (Fig. 2).

Single plane radium implantation for a squamous epithelioma of the tongue (Fig. 3).

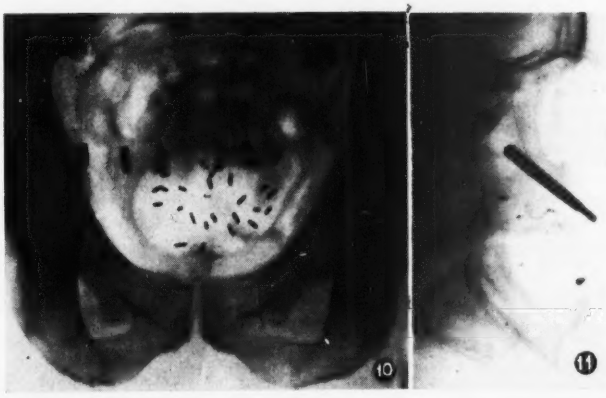
Volume radium implantation of the tongue and the floor of the mouth (Fig. 4).

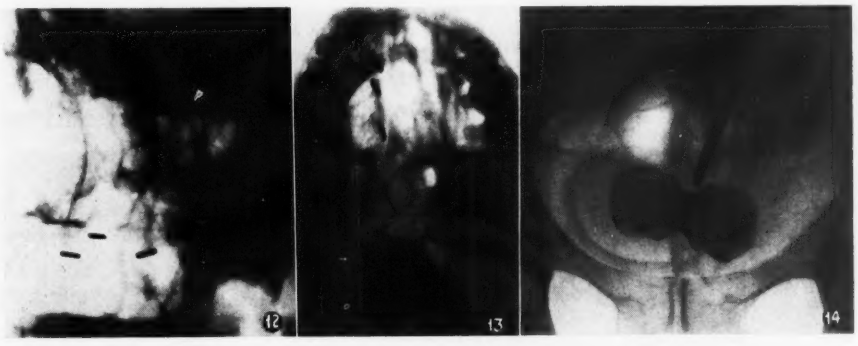
Implantation with radium needles spaced according to the distribution rules of Paterson and Parker for a scirrhous cancer of the breast with involvement of axillary glands (Fig. 5).

Single plane implant for a carcinoma of the bladder (Fig. 6).

Radon seed implantation for a cavernous haemangioma over the upper end of the sternum in a baby of 3 months (Fig. 7). I am indebted to Sir Stanford Cade for demonstrating the use of the specially long seeds in the treatment of these haemangiomata.

Radon seed implantation for the treatment





of squamous carcinoma of the right tonsil (Fig. 8). Note the difference in the size of the radon seeds as compared with Fig. 7.

Radon seed implantation for an epithelioma of the soft palate (Fig. 9).

Radon seed implantation into 2 separate malignant growths of the bladder (Fig. 10).

Carcinoma of the left antrum involving the palate. Treated by radon seed implant into the palate and by X-rays to the antrum in 1950. Radio-active cobalt tube inserted into the antrum by Mr. W. Kerr in 1955 (Fig. 11).

Implantation of radon seeds into a nasopharyngeal fibroma in a male aged 16 years (Figs. 12, 13).

Manchester technique of radium treatment for a carcinoma of the cervix. Rubber ovoids with radium in the fornices and a central tube of radium in the uterus (Fig. 14).

Implantation of radon seeds into a carci-

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noma of the bronchus according to the method of Ormerod[16] (Fig. 15). The appearance of clumping of the radon seeds is due to their being in different planes.

Radon seed implantation into a large malignant ulcer of the posterior third of the tongue in a man aged 71 years. Radon seeds were used because this site is unsuitable for radium implantation (Fig. 16).

Radio-active cobalt in an oesophageal applicator (3 tubes containing a total of 105 mc.). The patient, a male of 71 years, had a carcinoma of the oesophagus (Fig. 17).

OPSOMMING

Beskerming van afwisselende oppervlaktes van die vel laat behandeling met groter dosisse X-strale toe, en gevolglik is daar 'n groter uitwerking op diepgeleë gewasse.

Bestraling deur die openings van 'n spesiale rooster of sif het dit moontlik gemaak.

Rooster-behandeling gee reaksies soortgelyk aan dié verkry met standaard-radioterapie, en verbeter die dieptedosisse wat toegedien kan word. Dit word die arm man se plaasvervanger vir superstroomspanning en rotasieterapie genoem.

Die nadele daarvan is die verlenging van die behandelingstyd en die gevolglike onkoste om die apparaat aan die loop te hou; maar die onkoste is veel kleiner as in die geval van superstroomspanningterapie.

Ander stralingsbronne is die radiumbom (vir uitwendige doeleindes), radiumplate (vir vlakgeleë letsels), radiumbuise (vir binne-holte-gebruik) en radiumnaalde (vir tussenselruimte-behandeling). Radon (die ontbindingsproduk van radium) word ook gebruik, bv. vir kanker van die tong, wang, blaas en ander bereikbare liggaamsdele.

Radio-aktiewe kobalt word op dieselfde manier as radium gebruik, in die vorm van 'n bom of as naalde.

'n Paar van die maniere om radium, radon en radio-aktiewe kobalt aan te wend, word geïllustreer.

Some of the implantations were done in collaboration with surgical colleagues to whom we express our grateful thanks:

Case 6 (Fig. 6) with Mr. S. J. Hoffman; Cases 8, 11 and 12 (Figs. 8, 11–13) with Mr. W. Kerr; Case 10 (Fig. 10) with Mr. R. D. Venn; Case 15 (Fig. 15) with Mr. G. R. Crawshaw; Case 16 (Fig. 16) with Mr. B. Bernstein; Case 17 (Fig. 17) with Mr. Monte Jackson.

We are also indebted to Dr. E. Samuel and to Drs. M. H. Fainsinger, D. R. Morris and H. Jackson for the various radiographs.

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(To be continued)

SWELLINGS OF THE NECK

LYMPH GLANDS

JAN H. LOUW, Ch.M.* ·

and

C. F. M. SAINT, C.B.E., M.D., M.S., F.R.C.S., Hon. F.R.A.C.S., Hon. F.R.S.M.†

Department of Surgery, Medical School, Mowbray, C.P.

(Continued from p. 17)

(d) *Tuberculosis.* Tuberculous cervical lymphadenitis is still very common in South Africa, especially in the non-European population. In the African the human bacillus is almost always the causative factor. The disease occurs in 3 main clinical groups.

i. *Tuberculosis of the Upper Cervical Lymph Nodes.* The great majority of infections occur in childhood through the lymphoid tissue of the bucco-pharyngeal mucosa. The affected glands therefore usually belong to the upper deep cervical group, especially the 'tonsillar' gland in the region of the carotid bifurcation (Figs. 11, 12). In more than half of these cases the tonsils are obviously diseased and many show microscopic evidence of tuber-

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Fig. 11 (*Left*). A typical example of tuberculosis of the 'tonsillar' gland. The swelling (of two months' duration) was firm, smooth and fairly well defined.
Fig. 12 (*Middle*). Tuberculosis of the 'tonsillar' gland of 3 months' duration. The swelling has become fluctuant and commenced to point.
Fig. 13 (*Right*). Tuberculosis of the pre-auricular glands simulating a parotid swelling.

Fig. 14 (*Left*). Tuberculosis of the occipital glands with involvement of the overlying skin.
Fig. 15 (*Middle*). Tuberculous submental glands which have become matted together.
Fig. 16 (*Right*). Tuberculous submandibular glands simulating a swelling of the submandibular salivary gland.

culosis. Occasionally the pre-auricular (Fig. 13) or occipital glands (Fig. 14) are the first to enlarge and in such cases the adenoids sometimes reveal the presence of tuberculosis. Less frequently the submental (Fig. 15) or submandibular (Fig. 16) glands may enlarge before the others.

In the early stages the affected gland is firm and elastic in consistency, smooth and discrete, but extension commonly takes place to neighbouring glands which become matted together to form a large, lobulated swelling (Fig. 17). At this stage central destruction has usually occurred, although fluctuation can-

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not yet be detected. In neglected cases further extensions may occur to any or all the glands in the neck.

Fig. 17. Extensive tuberculous involvement of the upper deep cervical glands which have become matted together to form a large, firm, lobulated swelling.

The subsequent progress varies. A fair proportion of the glands retrogress and may be rendered quiescent or cured with or without fibrosis and eventual calcification. More commonly, however, suppuration occurs and this is very frequently due to secondary pyogenic infection from the pharynx. Indeed, once a tuberculous tonsillar gland has reached the size of a walnut, it is rare for suppuration *not* to occur. This results in the development of fluctuation and very soon the overlying skin becomes adherent and pink and somewhat cyanotic in colour (Fig. 18). If such an abscess is not promptly treated, the overlying skin becomes wrinkled and bluish and pus discharges on the surface (Fig. 19). Following discharge, secondary pyogenic infection is likely to take place, if not already present, and to lead to persistent sinuses (Fig. 20), scrofuloderma (Fig. 21) and keloid formation (Fig. 22).

Usually the affected glands are deep to the cervical fascia under cover of the sternomastoid. When pus forms, it penetrates the fascia and reaches the surface in front of or (less commonly) behind the sternomastoid; sometimes even at a distance from the initial focus, so forming the superficial loculus of a dumbbell or collar-stud abscess (Fig. 23). At times the infection extends into and through the muscle and in such cases a narrow track connects the deep focus with the subcutaneous

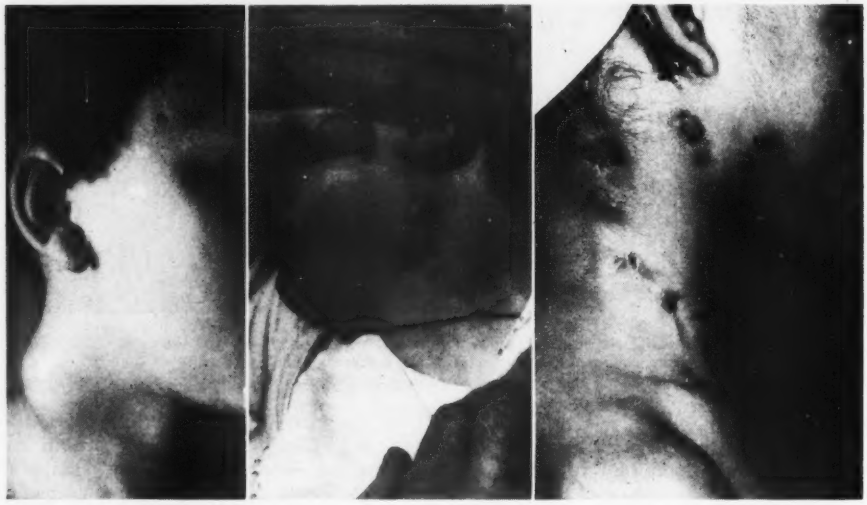

Fig. 18 (*Left*). Fluctuating cold abscess secondary to tuberculosis of the upper deep cervical lymph nodes.
Fig. 19 (*Middle*). Tuberculous glands which have broken down and discharged on the surface.
Fig. 20 (*Right*). Multiple tuberculous sinuses secondary to cervical gland involvement.

Fig. 21 (*Left*). Extensive scrofuloderma following tuberculous cervical lymphadenitis.
Fig. 22 (*Right*). Keloid formation in the scars of healed tuberculous sinuses.

Fig. 23 (*Left*). A typical tuberculous collar-stud abscess. The affected glands are situated deep to the sternomastoid and pus has tracked through the deep fascia to point superficially behind the muscle.
Fig. 24 (*Middle*). An unusual type of tuberculous collar-stud abscess. Pus has tracked through the sternomastoid itself to point superficially.
Fig. 25 (*Right*). A cold abscess extending diffusely within the sheath of the sternomastoid, secondary to tuberculous glands which have ruptured into the muscle.

abscess (Fig. 24). As a very rare event, the tuberculous infection may extend diffusely in the muscle belly and produce a condition the exact counterpart of a psoas abscess secondary to tuberculosis of the spine (Fig. 25).

ii. *Tuberculosis of the Lower Cervical*

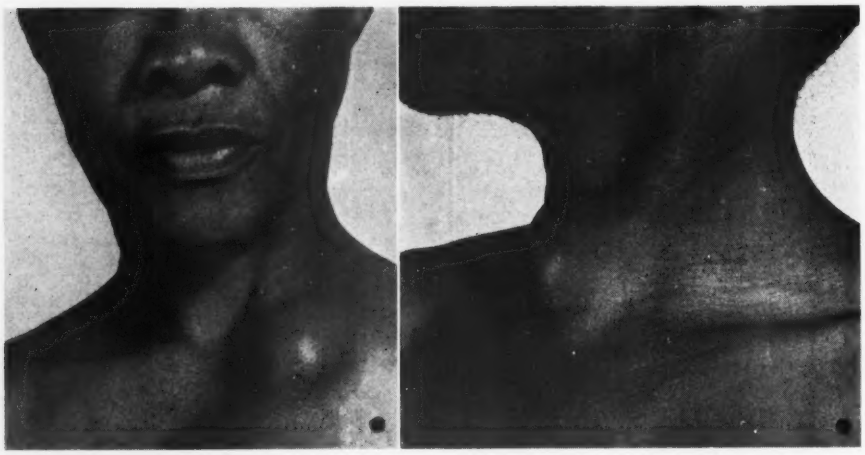

Fig. 26 (*Left*). Tuberculosis of the lower deep cervical (supraclavicular) glands secondary to tuberculosis of the lung apex. In such cases the overlying pleura is involved.
Fig. 27 (*Right*). Tuberculosis of the anterior group of lower deep cervical glands due to upward extension of the disease from the mediastinal glands.

Fig. 28 (*Left*). Diffuse hypertrophic tuberculosis of the cervical glands. Note the biopsy scar.
Fig. 29 (*Right*). Diffuse hypertrophic tuberculosis of the neck glands producing the typical bull-neck appearance. Some of the glands have broken down with sinus formation.

Lymph Nodes. In childhood, tuberculosis of the lower cervical nodes is much less frequent. In older patients, however, infection of the supraclavicular nodes is quite common (Fig. 26). In these cases the primary focus is usually in the lung apex with pleural adhesion and subsequent drainage to the glands in the neck. This observation is important from the therapeutic point of view, since the glandular enlargement indicates involvement of the apical parietal pleura with adhesions which are not likely to permit of apical collapse by artificial pneumothorax. The affected glands, which are situated deep to the sterno-

XUM

Fig. 30. Diffuse hypertrophic tuberculous lymphadenitis with an unusual tuberculide of the skin (proven by biopsy).

mastoid insertion, behave very much like those in the upper deep cervical group, although extensive suppuration and sinus formation are less frequently seen.

In other cases, the enlarged glands appear medial to the inner border of the sternomastoid (Fig. 27). In these cases the disease has usually extended upwards from the mediastinum.

iii. *Diffuse Hypertrophic Tuberculous Lymphadenitis.* This type is uncommon in young children and in White and Coloured races. Characteristically it occurs in African adolescents and young adults. There is diffuse involvement of several gland groups, cervical and elsewhere, probably due to blood-borne infection. These cases may be examples of the tendency of tuberculosis to involve articular tissues or organs.

The affected glands are large and elastic and remain discrete and movable for long periods, although they may become matted together to form large, lobulated, rubbery swellings, which later break down. In the cervical region this results in a characteristic bull-neck appearance (Figs. 28-30). Splenomegaly may occur, the blood picture is often not characteristic, and the differential diagnosis from Hodgkin's disease is often impossible without biopsy.

OPSOMMING

Die kliniese verslag oor kroniese ontstekingswelsels van die limfkliere in die nek word afgesluit met 'n oorsig van tuberkuleuse limfadenopatie.

(To be continued)

SKELETAL CHANGES IN ENDOCRINE AND METABOLIC DISORDERS

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II. CRETINISM

Skeletal changes in cretinism are frequently quite characteristic and may be valuable aids in diagnosis.

In the young infant, when diagnosis is notoriously difficult, the outstanding feature is delay in ossification and in appearance of epiphyses. The metaphyseal zones of provisional calcification may be unusually dense.

In childhood bone age is, of course, years behind the chronological age, and the late-developing epiphyses are characteristically irregular and fragmented. Involvement of the hips is indicated clinically by coxa vara, waddling gait and incomplete range of movement.

Radiologically the femoral epiphyses are typically flattened, ossify from multiple small irregular dense centres and when they fuse in adult life they remain markedly abnormal in shape (Fig. 1).

In the developing stage a single X-ray picture may mimic Legg-Perthes' disease, though the sequence of events is different. '*Bilateral* Legg-Perthes' disease' should always lead one

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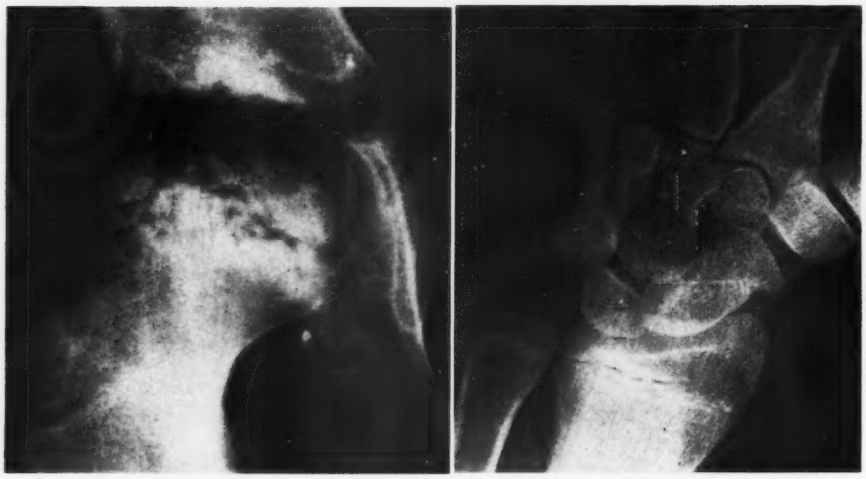

Fig. 1. Irregular fragmentation in epiphysis for femoral head in a cretin aged 18.
Fig. 2. Delayed epiphyseal union in a male cretin aged 26.

to suspect cretinism. Other conditions in which the epiphyseal dysgenesis may be similar are Morquio's disease and Multiple Epiphyseal Dysplasia.

The spine may show irregularities of the outline of the vertebral bodies, partial wedging of some vertebrae and kyphoscoliosis. Sometimes the first lumbar vertebra is very small and displaced backwards, leading to a localized kyphos. The same phenomenon may be seen in achondroplasia, Morquio's disease and gargoylism. Like these conditions, cretinism is, in fact, a developmental chondrodystrophy.

Fig. 3. Female cretin aged 56, showing coxa vara and flattening of femoral head, while the secondary epiphyses of the ischio-pubic area are still unfused.

In adult life bony fusion is so delayed that some epiphyses may be open until 30–40 years of age, or later, e.g. vertebral plates, wrist, ischio-pubic area (Figs. 2, 3). The iliac crest is particularly late in fusing. The skull is long (dolichocephalic) and heavily ossified with distinctly marked sutures, a thin anterior fontanelle region and a large sella turcica.

In *juvenile hypothyroidism secondary to hypopituitarism* a similar chondrodystrophy with grossly delayed bone age is uncommon. In general the bones are lighter and tend more towards osteoporosis, while the pituitary fossa will not be large unless distorted by a mass. Differentiation between primary and secondary hypothyroidism will, however, depend mainly on endocrinological features.

OPSOMMING

Die skeletveranderings wat kretinisme vergesel, kan help met diagnose by die suigeling, die jong kind en die volwassene.

Weerskantige fragmentasie van die heuplitte is 'n opvallende kenmerk van hipertiroïdisme gedurende die ontwikkelingstydperk.

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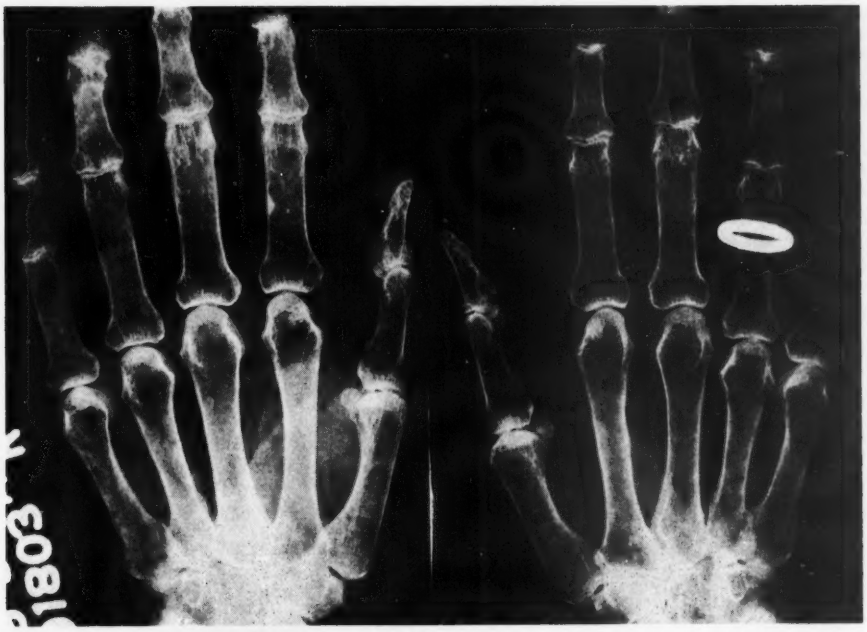
III. THYROTOXICOSIS



Figs. 1, 2. Gross decalcification with cortical thinning in a thyrotoxic woman of 60 who was bedridden from back pain and femoral fractures.

It is not very widely realized that demineralization may be an outstanding feature of thyrotoxicosis, although this was known to Askanazy [1] in the last century. The decalcification seems to affect all bones, but it may be especially evident in the spine, leading to compression fractures, changes in vertebral shape, loss of height and back pain. The serum calcium, phosphorus and phosphatase are normal, so that primary osteoporosis may be diagnosed if the thyrotoxicosis is not suspected. Furthermore, the type of thyrotoxic patient liable to thinning of bone is the slow, smouldering case, without gross signs, which goes unrecognized for a matter of years. One patient, a male fish freezer, aged 50, had been known to have had a porotic spine for 10 years, and the 24-hour urine calcium content on 2 occasions had been over 400 mg. Recently he had developed a myopathy, and a rapid pulse, warm skin and enlarged thyroid gland were noted. Serum protein-bound-iodine was 12.4 γ per 100 c.c. (normal maximum, 8). His symptoms were entirely relieved by a dose of radio-iodine (I^{131}).

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If a post-menopausal patient develops unusually severe osteoporosis, a masked thyrotoxicosis may be present as well. The woman whose X-rays are depicted here (Figs. 1, 2) actually had obvious thyroid disease with loss of weight, sweating, tremor, thyromegaly and exophthalmos. The symptoms of which she complained, however, were back pain and leg fractures.

The cause of the demineralization appears histologically to be a mixture of osteoporosis, osteitis fibrosa and osteomalacia,[2] though the changes in blood chemistry usually found with the last two are not seen. Theoretically one can imagine osteoporosis occurring from lack of available protein following excessive general body catabolism and nitrogen loss, or osteitis fibrosa from excessive catabolism of bone itself; perhaps excessive loss of phosphorus might be associated with osteomalacia.

OPSOMMING

Skildkliervergiftiging kan in verband gebring word met die taamlike ernstige ontmineralisering van die bene, veral as die siekte van die kroniese, okkulte soort is.

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IV. CARCINOMA OF THYROID

Thyroid cancer is of two main types, papillary and non-papillary.

The papillary neoplasm is very slow growing, of low malignancy, found not infrequently on routine section imbedded in a nodular goitre. It is locally invasive, but seldom or never gives rise to distant metastases when left alone.

Of the non-papillary neoplasms, the adenocarcinoma is still a relatively slow-growing tumour, with a particular tendency to metastasize to bone. The bone lesions are osteolytic in nature. These metastases may be metabolically active and rarely even produce thyrotoxicosis after the thyroid gland has been totally removed. Many of them will take up iodine from the blood stream and so may be discovered or treated by radio-iodine (I^{131}).

Of course, no other bone lesion will accumulate iodine, so that a positive test is completely diagnostic of secondary thyroid deposit.

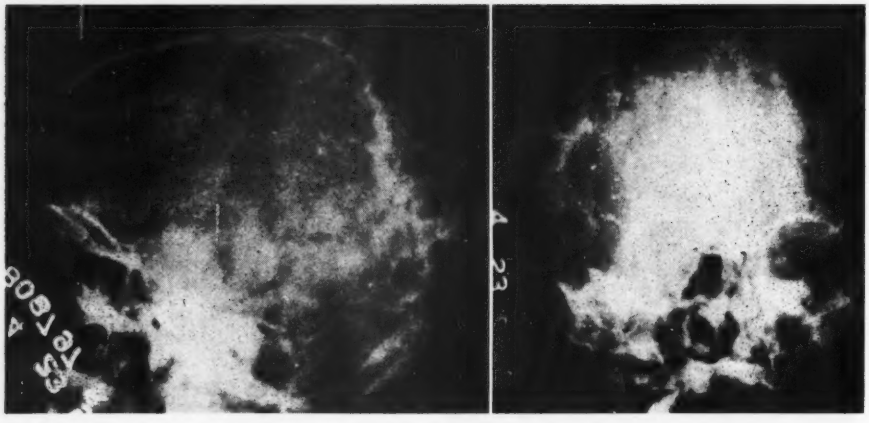

Fig. 1. Metastasis from adenocarcinoma of the thyroid, which accumulated iodine after a tracer dose. There is an unusual amount of calcification in this deposit.

OPSOMMING

Die vernaamste soorte karsinome van die skildklier en die been-metastase word genoem.

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SYMPATHETIC NEURINOMA

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A case of neurinoma arising from the cervical sympathetic chain is recorded. These tumours are not uncommon, the one here noted being distinguished only because of its size. Its removal was characteristically easy, division of the superior thyroid vessels permitting a plane of cleavage to be found so that the mass could be removed without difficulty.

CASE REPORT

J. W., an European male aged 48, complained of a lump in the neck present for the last 27 years. It had started as a small nodule in the left side of the neck in the region of the side of the thyroid cartilage, causing no pain or discomfort. It grew very slowly. About 7 years after its appearance, the patient was operated upon and was afterwards told that the tumour had contained blood and that it was irremoveable. He was advised never to let anyone meddle with the lump and was perfectly contented to carry on for 20 years more.

At no time had there been any pain, nor was there any difficulty with swallowing or with breathing. He was a fruit hawker and this kept his voice in fine fettle; he found it completely adequate for his needs.

Ten months before admission an attempt was made to throttle him. Since then the lump had grown rapidly and it was this recent increase in size that had compelled him to come up for treatment.

He was a well-built man in very good general condition. The heart, lungs and central nervous system were normal. There was a left Horner's syndrome. The voice was normal. In the left side of the neck was a mass about the size and shape of a large coconut which extended from the lower border of the jaw and ear above, to the clavicle below, and from the midline anteriorly to the trapezius posteriorly. The consistency of the mass varied from rubbery hard to fluctuating, its surface was smooth and its edges were well defined (Fig. 1). Running along the lateral surface of the mass and plainly visible beneath the skin were the common, internal and external carotids. The sterno-mastoid was displaced laterally and backwards so that its upper and lower ends only could be palpated. The trachea and thyroid cartilage were pushed well over to the right side so that the latter structure came to lie under the right angle of the jaw. The lump extended under the left angle and horizontal part of the jaw which appeared to be splayed out over it; below, it lay squarely on the clavicle and the left thoracic inlet, but it could be lifted up slightly. There was no expansile impulse and no bruit could be heard. No other lumps were palpable in the neck.

A needle inserted into 2 places drew dark bloodly material resembling fluid from an old haematoma.

X-rays showed that the trachea and oesophagus were displaced over to the right side and that the angle of the lower jaw was flattened out over the soft tissue shadow. The left upper ribs were crowded together.

Because of the situation of the mass lateral to the trachea and medial to the carotids, and because of its slow rate of growth, the preoperative diagnosis lay between:

(a) A carotid body tumour;
(b) A branchial cyst with haemorrhage;
(c) Sympatheticoblastoma.

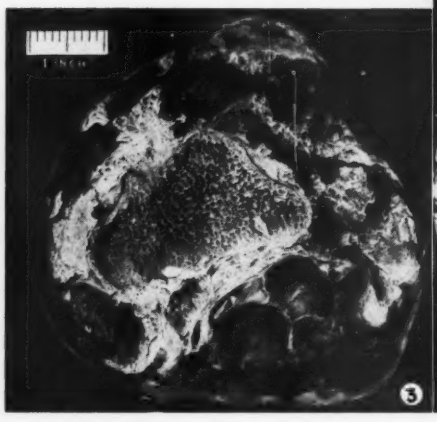
An operation was performed on 6 August 1941; anaesthesia was induced with gas and

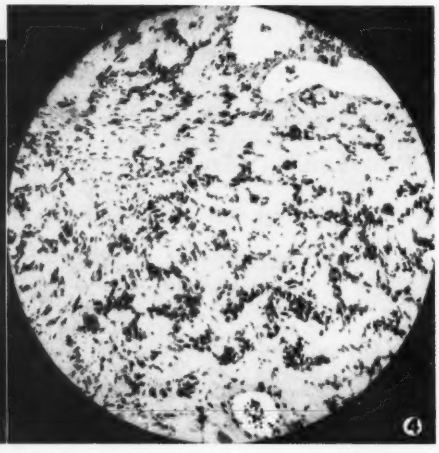
oxygen and maintained, after the introduction of an intratracheal catheter, with this and a little ether by Dr. H. van Niekerk.

A 'Z'-shaped incision was made along the lower margin of the jaw, from the mastoid process to the sterno-clavicular joint and along the inner half of the clavicle. The 2 flaps thus marked out were elevated and the anterior border of the sterno-mastoid was defined along its full length. The carotid arteries were now exposed and the vertical portion of the incision was deepened, veins being divided as they were encountered. It was necessary to ligate and cut the superior thyroid vessels and once this was done, the thyroid could easily be separated from the mass. After some dissection a plane of cleavage was found and it was then noticed that the tumour occupied a very definite fascial plane and that the whole vascular tree in the neck could be lifted up easily from the mass, which was shelled out.

After the mass had been removed, the trachea and the carotids assumed their normal positions although there was a considerable apparent redundancy of both structures. The internal jugular vein was seen on the lateral side of the space close to the carotid system. Neither the sympathetic nor the vagus were seen nor were they searched for. The very loose skin was now closed with clips and a pack of flavine in oil was put into the large cavity left behind.

The post-operative course was completely uneventful. The Horner's syndrome persisted. There was no alteration in the voice. The carotids could be felt pulsating in their normal position after the immediate post-operative period had passed. The patient was discharged 4 weeks after operation (Fig. 2), and is still alive and well (June 1955).





Pathological Findings. The specimen was a rounded mass 15 cm. in vertical length, 10 cm. in antero-posterior length and 10 cm. thick. It was perfectly smooth except on its outer surface which presented a 'Y'-shaped groove which had been occupied by the common, internal and external carotid arteries. On section, its cut surface showed masses of haemorrhage into the tumour, which was represented by a thin layer of tissue immediately under the capsule (Fig. 3).

Microscopy Report (Prof. B. J. Ryrie): Neurinoma (Fig. 4).

SUMMARY

A case of a neurinoma arising from the cervical sympathetic chain is recorded.

It was removed.

OPSOMMING

'n Geval van nuerinoom voortspruitende uit die simpatiese nekketting word beskryf.

Dit was verwyder.

I have to acknowledge with thanks the courtesy of my erstwhile chief, Mr. W. Lennox Gordon, F.R.C.S., who gave me permission to treat this patient.

SPINAL OSTEOPHYTES

REPORT OF A CASE ASSOCIATED WITH DIFFUSE ATHEROSCLEROSIS AND OSTEITIS DEFORMANS*

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The clinical significance of cervical osteophytes has only been fully recognized in recent years. In the present case, followed for 15 years, a diagnosis of cervical osteophytes has now been made. The patient in the course of his illness presented many interesting features and problems. His illness is now complicated by the super-imposition of another disease—Paget's osteitis deformans.

Mr. E. F., aged 75 years, complained on 21 July 1954 of severe pain (at the lower end of the spine) present for 6 weeks and aggravated by any movement of his back; although, once in a fixed position, he was reasonably pain-free. The pain radiated bilaterally round over his glutei and disappeared into the area of the inguinal ligament. Since the onset of the pain he has been unable to straighten his back.

His family history was non-contributory. He was born in England, had been a commercial traveller, but had not come into contact with any known toxic agents. Although accustomed to his 'daily spots', he had not had any alcohol for many years. Formerly a heavy pipe smoker, he now smoked about 12 cigarettes a day.

In 1933 he had fallen onto his neck in a fainting fit, and had shingles on the back and chest. In 1936 he suffered from lumbago for 2 - 3 days after lifting a heavy weight. In 1938 he fell on to his right shoulder. In 1942 he had pleurisy.

In 1939 he noticed that his left upper arm was weak, was wasting and that the muscles were twitching. Pain radiated down the upper outer aspect of the arm and was aggravated by cold, wet and movement. The wasting was most marked in the deltoid, triceps and biceps muscles. The right upper limb was minimally affected and the lower limbs were intact. A full blood count and lumbar puncture were quite normal. Radiography of the neck revealed a deformity of the third cervical vertebra consistent with an old crack fracture. There was marked osteoarthritis of C5 - 7 vertebrae with narrowing of the joint spaces. The electrical reactions were normal. A diagnosis of atypical progressive muscular atrophy was made. Physiotherapy was instituted and improvement was reported.

In February 1944 he complained that for the past year his legs had been becoming stiff. Examination revealed a spastic paralysis of both legs with bilateral extensor plantar responses. There were questionable signs of posterior column loss in both lower limbs with hypo-aesthesia and hypo-algesia extending up to the D7 segment. In the upper limbs the previous signs were more advanced. The reflexes in the upper limbs were present, normal and equal and those in the lower limbs markedly increased. The upper abdominal reflexes were weak, the lower ones absent. There were prominent veins over the abdomen and the liver was 3 - 4 fingers enlarged, tender and hard. Radiography revealed fusion of the bodies of C5, 6 and 7 vertebrae, associated with marked osteoarthritis in both the cervical and lower dorsal spines.

In 1945 he began to complain of a dull pain in the pelvic and lumbar areas. Paraesthesiae were present in the left foot as well as painful spasms of both legs. He had difficulty in controlling his urine when standing, and there was urgency and dribbling. A lumbar puncture in August 1945 revealed no block. The protein content was 100 mg. per 100 c.c.; no other abnormalities were found. A gastric analysis revealed an almost complete achylia. At this stage subacute combined degeneration was diagnosed and the patient treated with ventriculin, hydrochloric acid and iron orally.

A lumbar puncture in December 1945 revealed a protein content of 80 mg. per 100 c.c. During 1946, his condition remained unchanged. In December 1946 the blood count revealed a slight normocytic anaemia, but no other abnormality. He was not seen again until his present admission.

His condition had slowly and steadily

* A paper read at a Clinical Meeting at Tara Hospital, Johannesburg.

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deteriorated. He had lost about 10 lb. in weight. He stated that his 'pelvis seemed too weak to support' him. He felt full of energy but could not move because of his physical incapacity. His symptoms were worst in the early morning, improving as the day advanced. He had frequency and urgency of micturition in the first 2 hours after rising, but not during the remainder of the day.

He was a thin bent man with a spastic shuffling gait walking with the aid of 2 sticks.

The cranial nerves were all intact. The upper extremities were markedly wasted (especially in the proximal segments) and fibrillation was present. Power was surprisingly good when compared to the degree of wasting. The loss was most marked in the shoulder girdle muscles. Tone was bilaterally increased with a definite cogwheel element on the right. On holding both upper limbs extended, the right hand flexed involuntarily at the metacarpophalangeal joint. Purposive movements were impeded by the hypertonus. There was an inconstant pill-rolling tremor, which disappeared on voluntary movement, associated with the typical 'Parkinson hand' on the right side.

There were comparable findings in the lower limbs, the hypertonus being far more marked and of purely pyramidal type. Painful flexor spasms occurred frequently during examination, but the patient stated that they were not usually so marked. There was loss of vibration sense below both elbows and bilateral impairment of joint sense in the fingers, more marked on the right. In the lower limbs vibration sense was diminished below the knees and joint sense impaired bilaterally in the toes, again on the right more than the left. There was no sensory involvement of the trunk.

The reflexes were as follows: slight jaw jerk, markedly exaggerated and bilaterally equal biceps, triceps and supinator jerks and bilaterally positive finger jerks. No abdominal reflexes were obtained. The knee jerks were markedly increased and clonus was present. The ankle jerks showed merely a normal response. Bilateral Babinski responses were present.

The spinal curvature showed several changes. There was loss of the normal cervical lordosis, thoracic kyphosis and lumbar lordosis with an acute kyphos at the lumbo-sacral junction. This straight spine was further complicated by a lower thoracic scoliosis. There was marked limitation of spinal movements at all levels but (apart from the lumbo-sacral region) these were painless. There was no tenderness over the spinous processes but 'deep pain' was present over both glutei.

Examination of the head and neck revealed a small xanthoma above the inner canthus of the left eye, bilateral early cataracts and a bilateral arcus senilis.

The heart and lungs were normal clinically. The blood pressure was 200/120 mm. Hg. The extremities, particularly the feet, were cold; all the peripheral pulses were palpable but the vessel walls were clearly thickened. The fundal vessels were arteriosclerotic.

A left indirect inguinal hernia was noted. The liver edge was tender and just palpable. There was a prolapse of the rectum (present for about 12 years) with surrounding superficial erythema and scaling of the skin. A lipoma was present over the left ilieum and there were a few scattered pigmented naevi and papillomata on the trunk.

He was a friendly, euphoric, co-operative man who gave a fairly good account of himself, and although his memory was not always correct about dates, there was no marked impairment. Emotionally he was somewhat labile but his affect was congruous. His insight and judgment were intact and his intelligence good. He had a healthy attitude to his illness and helped his wife in running a nursery school, by sitting in a chair and talking and telling stories to the children.

SPECIAL INVESTIGATIONS

A full blood count was normal. Wassermann reaction, negative. The plasma inorganic phosphorus, urinary calcium, serum acid phosphatase, serum calcium and potassium were all within normal limits. The serum alkaline phosphatase was raised (17 King-Armstrong units).

The blood urea was normal. The urine examination revealed no abnormalities and the urea clearance test indicated 70% of average normal renal function. The urine concentration and dilution tests revealed a maximum concentration of 1024 and a minimum dilution of 1000.

Lumbar puncture revealed a very low pressure (the patient had to be sat up) but there was no block, the only abnormality on analysis being a protein content of 110 mg. per 100 c.c.

The gastric analysis was normal.

Radiography proved to be extremely interesting. Very marked changes of Paget's disease were present in the pelvis but there was no evidence of malignant degeneration (Fig. 1). The lumbar spine showed evidence of Paget's disease involving the bodies of the fourth and fifth lumbar vertebrae; marked osteoarthritic changes were present. There was gross narrowing of the disc spaces between the bodies of L2 and 3, L3 and 4 and L4 and 5 (Fig. 2). Osteoarthritic changes were present in the mid- and lower regions of the dorsal spine. The cervical spine showed a kyphotic curve, fusion of the C5 - 7 (Fig. 3), gross narrowing of the disc spaces between the

remaining vertebral bodies with osteoarthritic lipping, and osteophyte encroachment into the lateral foramina (Fig. 4). The skull showed some thickening of the whole of the vault, but not sufficiently marked to justify a diagnosis of Paget's disease. The tibiae revealed no definite evidence of Paget's disease, except for a small area of cortical thickening in the right tibia. Osteoarthritic changes were present in both knee joints.

The electrical muscle tests in the upper half of the body indicated normal responses to faradism except in the left rhomboid muscle, which showed ACC>KCC. In the lower limbs there was a partial reaction of degeneration of the common peroneal group, the rectus femoris and posterior tibial groups.

THERAPY

The patient was put on to Tolserol tablets, 1 gm. 3 times daily. This has been increased to 1.5 gm. 4-hourly. He has had physiotherapy and a course of deep therapy to his lumbosacral area.

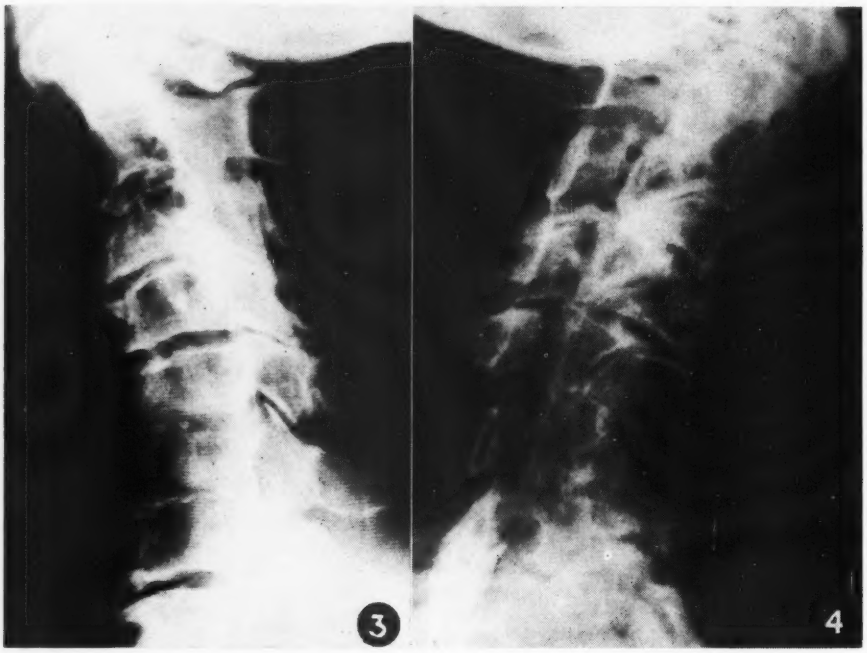
Symptomatically he has improved. The pain in his back is minimal and he can now once again walk fairly upright. He has learned to relax the muscles of his legs and his flexor spasms and gait have improved.

DISCUSSION

Allen[1] reports in detail cases operated on for the removal of cervical bony spurs. It is of interest here to briefly review some of these cases:

1. A man of 38 years with a 6-year history, who had in the course of his illness been diagnosed as an atypical progressive muscular atrophy.
2. A man of 73 years with a 10-year history, who had at one stage been thought to suffer from subacute combined degeneration and had achlorhydria.
3. A man of 36 years with a 6-year history, who had been diagnosed as a prolapsed cervical disc.
4. A man of 47 years who had had pain in the calves for many years but whose definite history extended for 1 year. A tumour at D12 was suspected and an exploratory operation did not reveal any pathology. More than a year later an operation for cervical osteophytes was undertaken on the evidence of new signs and symptoms.
5. A man of 45 years with a 15-month history, who simulated a unilateral progressive muscular atrophy.
6. A man of 44 years with a 6-month history, who was diagnosed pre-operatively as an angiomatous malformation of the cord with a solid tumour at about C6 - 7.

These cases in many ways simulate the history and picture of our patient. Initially a



diagnosis of atypical progressive muscular atrophy was made in the presence of purely motor involvement of the left upper limb and to a lesser extent of the right. Six years later the picture seemed to simulate a spinal cord tumour and the following year the presence of an achylia gastrica suggested subacute combined degeneration.

The differential diagnosis on the present admission was as follows:

i. *Cervical Osteophytes.* The gross osteoarthritic formation in the spine made reasonable an assumption that there was probably a considerable amount of root compression, especially in the cervical area. This has remained primarily affecting the upper cervical roots. The mechanism of the paraplegia is well described in Allen's article. He points out that pain is infrequent and not a marked feature when the cord is involved.

ii. *Subacute Combined Degeneration.* The age of the patient, the course of the illness and the absence of posterior column signs apart from what could be explained on an arteriosclerotic basis, were against this diagnosis. (Subsequent blood count and gastric analysis excluded this diagnosis very definitely).

iii. *Amyotrophic Lateral Sclerosis.* Here again the age of the patient, the course of the illness and the complete absence of any cranial nerve involvement were against the diagnosis.

iv. *Chronic Arachnoiditis.* There was a known history of trauma, but the absence of cells in the cerebrospinal fluid, despite the raised protein and the small role played by pain until shortly before admission, were points against this condition.

v. *Atherosclerosis of the Anterior Spinal Artery.* It is well known that progressive paraplegia can result from degenerative changes within the cord. Brain[2] and Kinnier Wilson,[3] in particular, point out that varied clinical pictures may result, depending on the degree and localization of the arteriosclerosis. This patient does show evidence of widespread degenerative arterial disease—his mental state, his Parkinsonism, the fundal and peripheral blood vessel changes and the associated hypertension. The disc spaces in the cervical region which were not seen on X-ray 10 years ago, were certainly present in 1939 and their degeneration and disappearance is common in vascular lesions of degenerative type and unlikely to be due to Paget's disease. However, the history in arteriosclerotic spinal disease does not follow the pattern of this patient, where paraplegia was preceded by lower motor neurone changes in the upper limbs. His condition, too, has progressed extremely slowly for this to be the sole diagnosis. Paget's disease is commonly associated with arteriosclerosis and may thus directly or indirectly be a causative factor in the hypertension and mental state.

The X-rays, however, pointed to a further factor in the diagnosis. Paget's disease was not suspected, but it would appear that it could play a definite part in the symptomatology and clinical signs. It would account for his pain in the lumbar area and his sudden kyphos (associated probably with collapsing vertebrae). It can also explain (by severe compression of the nerve roots) his extensive reaction of degeneration in the lower limbs. Paget's disease, however, rarely causes paraplegia, while cer-

vical osteophytes and arteriosclerosis more commonly do.

The association between Paget's disease, osteoarthritis and atherosclerosis is well recognized but the nature of the relationship remains obscure. The aetiology of Paget's disease is still unknown. The condition may remain unsuspected for a long time and only be discovered accidentally. Burrows[4] states that whereas the patient is usually elderly before a clinical diagnosis can be made, early changes may start at about 40 years of age. Unfortunately, one cannot state for how long this patient suffered from osteitis deformans, as in the absence of a positive indication to do so, no X-rays of the pelvis and lumbar region were taken until the present admission.

It is difficult to assess in this patient the relative roles of Pager's disease, atherosclerosis and osteoarthritis. They probably all play a part in explaining the picture, but the degree of pathological damage caused by each cannot at present be delimited.

SUMMARY

A case of cervical osteophytes seen over 15 years and associated with extensive osteoarthritis of the spine, diffuse arteriosclerosis and Paget's disease is presented and discussed.

OPSOMMING

'n Geval van nek-osteofiete wat oor 'n tydperk van 15 jaar behandel is en vergesel gegaan het van uitgebreide been- en gewrigontsteking van die ruggraat, verspreide arteriosklerose en Paget se siekte, word ontleed en bespreek.

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EPIDEMIC FOLLICULAR KERATOSIS

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During the first few months of 1955 the author encountered in general practice in Johannesburg several patients presenting with a wide-spread papular erythematous eruption, unaccompanied by any appreciable constitutional disturbance, with a benign course and quite unlike the common exanthemata. The condition had not (to the author's knowledge) been described before in South Africa, and its nature suggested an infective causal agent.

The clinical features and the course of the disease have been discussed more fully in this Journal by Craig Cochrane and Loewenthal.[1] This article summarizes the author's impressions and records some interesting features noted in his cases.

Dr. L. J. A. Loewenthal (who kindly saw one of the author's cases) confirmed the condition as identical with that described in his series. He also drew attention to the paper by Bowers[2] describing a similar, but probably not identical, eruption in England; and to the description of a similar condition by Schuppli.[3]

CLINICAL PICTURE

Both children and adults appear to be affected. The usual presenting feature is the sudden appearance, often overnight, of a wide-spread erythematous papular eruption, the papules being deep-seated, firm and about $\frac{1}{8}$–$\frac{1}{4}$" in diameter.

Many are contiguous and look like sago grains. The rash starts on the buttocks and thighs (where it remains most marked) but spreads to all other parts of the trunk and limbs, including the palms and soles, and also slightly on to the face.

The flushed appearance in some cases is unaccompanied by any appreciable pyrexia. No enanthem has been noted and neither lymphadenopathy nor splenomegaly has been observed.

Constitutional upsets are absent or few, consisting of slight headache and a ''flu-like' feeling at the beginning, sometimes slight sore throat and perhaps some joint and muscle aches.

By the second to the third day the eruption has often become slightly violaceous in parts, with a typical area of blanched skin around most of the papules, especially on the limbs. Slight itching may be present, but is usually absent.

The papular component then becomes less marked and the rash fades, leaving numerous

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brownish stains. Many of these, on magnification, are seen to be studded with petechiae and some are frankly purpuric.

By the fifth to the seventh day keratinous plugs extrude from many of the follicles; this is especially marked on the thighs and outer arm, giving a rough feel to the skin. The violaceous discolouration may persist, especially on the buttocks, for 1–2 weeks, the skin returning to normal after about 2–3 weeks.

In Mr. W., seen in January 1954, the papular phase persisted for over a week, and showed a much more marked purpuric component.

Race. Two of the cases were in adult African males, both employed as servants in the same household, and living together in quarters on the premises. They delevoped the characteristic papular eruption on the same day and followed the typical course of the syndrome.

Fig. 1. H. S. aged 8 years. Sixth day, showing a follicular eruption on the thighs passing into the keratotic phase, and with erythema multiforme around the knees. *Fig.* 2. H. S., 7th day, showing a follicular keratosis of the arm with erythema multiforme on the elbow.

One case, a female (H. S.) aged 8 years, showed an interesting variation (Figs. 1, 2). She presented with the typical wide-spread papular eruption and a complete absence of any constitutional disturbance. On the fifth to sixth day, however, as the initial eruption was fading and passing into the keratotic phase, she developed a secondary papular eruption, symmetrically distributed around both knees and ankles, and on the dorsa of both wrists and elbows. The papules were larger, flatter and more superficial than those of the initial eruption and were, in addition, very itchy. This secondary eruption was seen by Dr. Loewenthal and was considered to be that of an erythema multiforme; it gradually faded, without treatment, over the subsequent week. The child had received no drugs which could have precipitated an allergic response.

M. S., a male sibling aged 11 years, who presented with an identical papular, follicular eruption on the same day, did not develop any secondary allergic manifestations.

Wassermann reactions were negative. They had each taken a course of laxative tablets, containing phenolphthalein, about a week before. However, re-administration of these tablets at a later date failed to produce any skin eruption. The possibility of a drug eruption could therefore be excluded.

EFFECT OF TREATMENT

This has been difficult to assess because of the small number of cases (8) involved and the benign course. Four patients had been treated with antihistaminics (on the assumption of an allergic skin eruption) and 2 had received Terramycin (one following administration of an antihistaminic). Three had received no treatment. No appreciable difference in the course of the skin eruption was noted.

LABORATORY INVESTIGATIONS

Only 2 cases (H. S. and M. S.) were investigated fully. In both cases the blood picture (reported on by Dr. H. B. W. Greig of the South African

Institute for Medical Research) showed a normal total white cell count, with a lymphocyte count of 52.5% and 50% (of 7,300 and 4,000 respectively); in one (M. S.) there was a mild absolute eosinophilia (7%). In addition, many lymphocytes were 'atypical, suggesting a virus infection or possible glandular fever'. The E.S.R. was normal. After 2 weeks, atypical lymphocytes were still numerous and after 3 weeks the blood picture had returned almost to normal, only about 10% of the lymphocytes being atypical.

The Paul-Bunnell test was negative (maximum titre 1:14) both during the acute and the convalescent stages.

The streptococcal antihaemolysin-O test was negative.

Rickettsial complement fixation tests against epidemic and murine typhus, tick bite fever, rickettsialpox and Q-fever were negative on both acute-phase and convalescent blood, as were the complement fixation tests against herpes simplex, mumps and lymphocytic choriomeningitis.

Suspensions of the stools in each case were inoculated by Dr. Malherbe (of the South African Institute for Medical Research) into cultures of monkey kidney and human prepuce. The absence of a cytopathogenic effect failed to indicate the presence of viral activity in the stools.

MORBIDITY

Although the number of cases was small, several noteworthy features were observed.

The occurrence of the eruption simultaneously in 2 Africans living together, and in 2 siblings (M. S. and H. S.) supports an infective or toxic etiology.

The household in which the African cases occurred, consists of 2 adults (Mr. and Mrs. A.), their 3 children aged 6 years, 5 years and 1 year respectively, the 2 African males (employed as cook and gardener respectively) and 3 adult African female servants. In addition a 7-year-old nephew (M. J.) was living in the house temporarily.

About 16–18 days after the appearance of the eruption in the Africans Mr. A. developed the typical papular follicular eruption, accompanied by mild constitutional symptoms. At about the same period, the nephew (M. J.) who had been removed from the affected household to his own home about 9–10 days before, also developed the characteristic eruption. (This case was not seen by the author, but by Dr. G. Berry, whose description of the eruption, however, is quite typical). The remaining members of the household were not affected.

In the remaining cases close contacts did not appear to be affected, nor could the condition be traced from contact with other cases (i.e. apart from the 2 possible exceptions mentioned above). A child who had slept in the same bed as one of the cases (M. S.) on the night before the latter developed the eruption, did not develop any illness.

It is likely that the eruption has been fairly wide-spread in Johannesburg, though at present the exact incidence is not known. Many cases may have been labelled 'allergic rash', chicken-pox, etc. In view of the benign symptoms and course they have not been investigated further.

ETIOLOGY

The limited number of cases observed and investigated does not permit the demonstration of any definite causal factor, though several significant observations were made.

A non-specific allergic response seems highly unlikely because the eruption appeared simultaneously in 2 siblings and also in the 2 Africans. The course of events in the household of Mr. and Mrs. A. may be highly significant. The occurrence of the condition in 2 members of the household about 16 days after the initial African cases (and more especially since one case (M. J.) had no further contact with the affected household for at least 1 week before his eruption appeared) supports the theory of an infective agent (with an incubation period of between 2–3 weeks) as the etiological factor.

If a toxin were responsible, it is difficult to explain why all the other members of the household, exposed to the same surroundings and similar hazards, did not develop the condition.

The fact that most cases have no history of contact with a similar case and that known contacts have not developed the condition, suggest 2 possibilities based on an infective theory:

i. The occurrence of numerous subclinical infections;

ii. The spread of the infective agent either by inoculation from some insect vector, or by the oral route, rather than by droplet infection. While no primary bite or lymphadenitis has been noted, the possibility of an insect vector cannot be excluded.

The presence of numerous atypical lymphocytes in the peripheral blood is also more suggestive of a viral than a bacterial etiology. The negative Paul-Bunnell tests, the absence of lymphadenopathy, splenomegaly, oral signs or pyrexia, in addition to the way in which the present outbreak occurred, all point against the condition being a variant of infectious mononucleosis. The failure to demonstrate viral activity in the stools does not exclude a viral etiology.

Attempts will in future be made to isolate an infective agent directly from the skin lesions.

XUM

The occurrence (in H. S.) of an erythema multiforme secondary to the initial papular eruption is noteworthy if one postulates a possible allergic response to a viral agent, similar to the mechanism suggested in the pathogenesis of the Stevens-Johnson syndrome and other variants of erythema exudativum multiforme.[4, 5]

One patient (Mr. W.) attributed his condition to having cleaned out a dirty aquarium about 2–3 weeks before. This is of interest in view of the suspicion by Bowers that the Cheltenham epidemic described by him might have been caused by the contamination of the town's water supply, when a certain reservoir was brought into action after several months' disuse. In the other cases seen here, however, inquiry failed to establish the possibility of a water-borne infective agent or toxin. Moreover, the appearance of cases here has been more scattered and has occurred over a longer period of time than the sudden, short outbreak described by Bowers.

On the available evidence it is thus considered that the present outbreak is probably due to a specific agent, possibly viral or rickettsial, though definite proof of this is lacking.

SUMMARY

The clinical features of an epidemic papular follicular eruption are described.

The condition has been seen in 2 Africans.

The occurrence of an erythema exudativum multiforme as a secondary phenomenon has been noted.

The presence of numerous atypical lymphocytes in the peripheral blood appears to accompany the skin manifestations.

On the basis of limited observations it is suggested that the outbreak is probably caused by an unindentified infective agent, possibly viral or rickettsial.

OPSOMMING

Die kliniese kenmerke van 'n epidemiese papilêre follikulêre uitslag word beskryf.

Hierdie toestand is by naturelle opgemerk.

Die voorkoms van erythema exudativum multiforme as 'n sekondêre verskynsel is ook reeds waargeneem.

Dit skyn asof die vel-manifestasie vergesel gaan van die aanwesigheid van talle atipiese limfosiete in die perifere bloed.

Op grondslag van beperkte waarnemings word daar aan die hand gedoen dat die uitbreek van die siekte waarskynlik aan 'n ongeïdentifiseerde besmetlike agens, bes moontlik van 'n virus- of rickettsiatipe, te wyte is.

I wish to acknowledge my thanks to Dr. L. J. A. Loewenthal for his helpful suggestions; and to Drs. H. B. W. Greig and Malherbe of the South African Institute for Medical Research for the laboratory investigations.

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HAEMATOLOGICAL CASE BOOK

I. MULTIPLE MYELOMATOSIS

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An African female aged 70 years complained of breathlessness on exertion, loss of appetite and vomiting for 5 days. No further details were obtainable from her.

She was a thin, old lady in no acute distress. There were no engorged neck veins, no orthopnoea and no oedema of the feet. The heart was clinically enlarged but there were no murmurs. Blood pressure, 125/65 mm. Hg. The lungs were clear. The liver and spleen were not palpable.

A blood count showed:

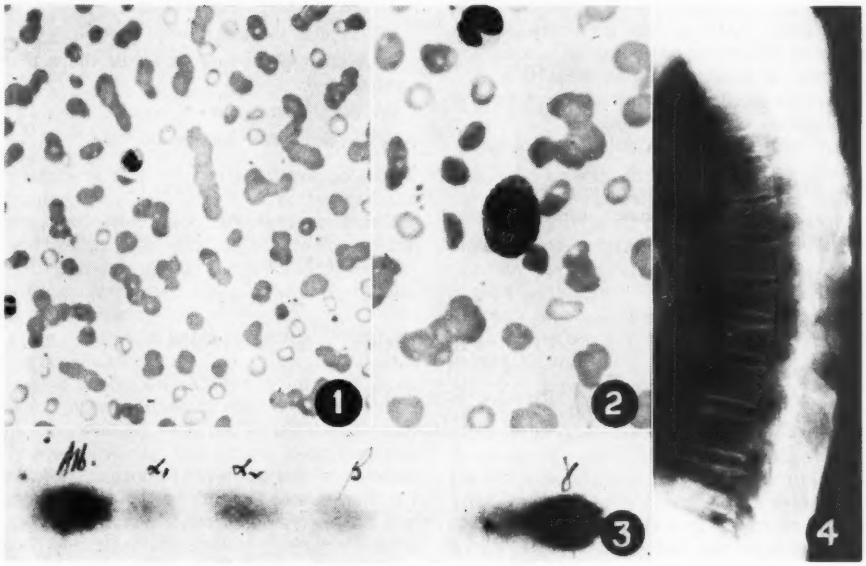

Fig. 1 Peripheral blood smear showing striking rouleaux formation.
Fig. 2. Peripheral blood smear showing a myelocyte.
Fig. 3. Paper electrophoresis strip showing very high gamma-globulin.
Fig. 4. X-ray showing osteoporosis and wedging of vertebrae.

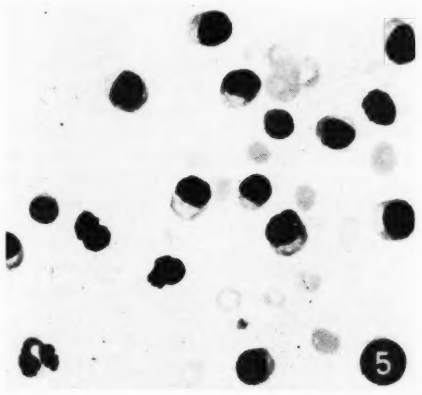

Fig. 5. Bone marrow smear showing a large number of plasma cells.

Haemoglobin: 5.8 gm.% (41% Haldane);
White cells: 9,000 per c. mm.;
Sedimentation Rate (Wintrobe's method): 77 mm. in 1 hour.

Examination of the film showed most striking rouleaux formation (Fig. 1) but little or no variation in size and shape. The differential count was normal (63% neutrophils, 27% lymphocytes) except for the presence of a few myelocytes and an occasional plasma cell (Fig. 2).

The myelocytes suggested the possibility of a space-occupying lesion of the marrow and the striking rouleaux formation suggested the possibility of multiple myelomatosis, a diagnosis to which the occasional plasma cell lent some faint support.

There were large quantities of Bence-Jones protein in the urine. The serum proteins were 10.8 gm.%, the albumin 1.6 gm.% and the globulin 9.2 gm.%, indicating a gross rise in serum globulin.

The zinc sulphate turbidity test was more than 15 units (normal 0-4) suggesting a much raised gamma-globulin. Paper electrophoresis showed a very high gamma-globulin (Fig. 3). The serum calcium was 7.5 mg. per 100 c.c. and the plasma phosphorus 4.0 mg. per 100 c.c. The blood urea was 107 mg. per 100 c.c. suggesting the possibility of a 'myeloma' kidney or of amyloidosis.

X-rays showed numerous punched-out areas in the skull and marked osteoporosis of the vertebrae with wedging in the mid-dorsal spine (Fig. 4).

XUM

On sternal puncture the bone marrow was hyperplastic. Almost all the cells present were well-differentiated plasma cells, a finding diagnostic of multiple myelomatosis (Fig. 5).

This case illustrates almost all the points in the diagnosis of myelomatosis.

1. A markedly raised globulin causing:
(a) Raised sedimentation rate.
(b) Marked rouleaux formation.
(c) High zinc sulphate turbidity test (gamma-globulin).
(d) Bence-Jones proteinuria.
(e) Typical electrophoretic pattern.

2. A space-occupying lesion of the marrow causing:
(a) Bone destruction.
(b) Leuko-erythroblastic anaemia.

OPSOMMING

'n Geval wat byna alle aspekte van die diagnose van miëlomatose toelig, word kortliks beskryf.

II. METASTATIC PROTASTIC CARCINOMA

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M. H., an African male aged 49, complained of pains in the hips, thighs and knees and inability to walk. He was somewhat unreliable but alleged he had had these complaints for about 2 weeks. He had to get up twice at night to pass water and had lost a fair amount of weight, but otherwise there was nothing else of note in the history.

He was a rather thin, old man looking much older than the stated 49 years. No abnormality of heart or lungs was noted. No abdominal masses were palpated. A fairly marked scoliosis and kyphosis were present as well as tenderness over the upper thoracic vertebrae. There was some oedema of the feet.

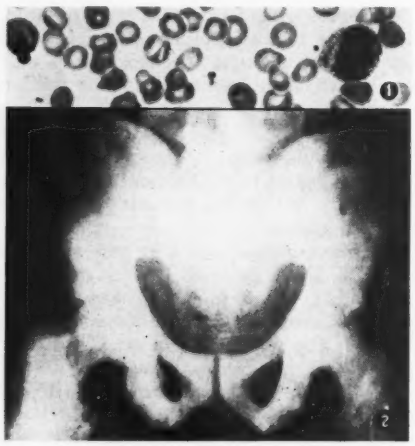

Fig. 1. Peripheral blood smear showing a myelocyte and a normoblast.
Fig. 2. X-ray of the pelvis showing sclerotic areas.

A blood count showed:
Haemoglobin: 6.3 gm.% (42% Haldane);
White cells: 8,000 per c. mm.

On examination of the stained film the red cells showed a little anisocytosis and poikilocytosis but nothing very specific. Many polychromatophilic cells were seen.

In spite of the normal total white cell count, there were some interesting abnormalities present. Although the differential count was fairly normal (55% neutrophils, 30% lymphocytes, 7% monocytes), a few normoblasts (nucleated red cells), myelocytes and an occasional myeloblast were present (Fig. 1). He therefore had a leuko-erythroblastic anaemia, i.e. an anaemia with primitive red and white cells in the peripheral blood. Among the common causes in this age group is a space-occupying lesion of the bone marrow such as secondary carcinoma.

An X-ray showed sclerotic areas in the vertebrae and pelvis highly suggestive of prostatic secondary growths (Fig. 2).

A rectal examination showed a stony-hard prostate, typical of carcinoma. The serum acid phosphatase was 120 King-Armstrong units (normal 1-3).

This is a typical case of carcinoma of the prostate, with secondary deposits in the pelvis and the verte'brae, causing a leuko-erythroblastic (or myelophthisic) anaemia.

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'n Tipiese geval van karsinoom van die prostataklier, met sekondêre neerslae in die bekken en die werwelbene wat aanleiding tot leuko-eritroblastiese bloedarmoede gegee het, word beskryf.

JUVENILE HYPOTHYROIDISM AS A CAUSE OF DWARFISM

A REPORT OF TWO CASES

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Dwarfism in childhood may present diagnostic difficulties as its causes are varied and numerous. Juvenile hypothyroidism offers the best hope of cure with timely treatment, but an understanding of the problem requires consideration of the factors involved in growth and development.

Growth (cellular multiplication) is basically concerned with change in size, i.e. with change in cell number, length, area, volume or mass, whereas development or differentiation affects structural changes.[1] Growth may be the more primitive attribute, but it acts in conjunction with differentiation in contributing to maturation.

During infancy and childhood, growth and development are affected by genetic, intrinsic and extrinsic factors. It is often difficult to determine which is of primary importance as they may overlap, e.g. the genetic factor may act directly on the tissues or indirectly by affecting the endocrine glands which then act on the tissues. The embryo may be affected pre-natally by extrinsic factors, e.g. infection, diet and X-rays. These may cause defects indistinguishable from those due to genetic causes. Even glandular dysfunction does not always contribute to dwarfism, but may be merely coincidental, e.g. ovarian agenesis and dwarfism; polyostotic fibrous dysplasia of bone and sexual precocity.

Extrinsic factors important in infant and child growth are caloric and vitamin intake (including utilization and assimilation) as well as adequate oxygenation of parts impaired by heart and lung disease.

Exclusion of genetic and extrinsic factors leaves the large group of endocrine problems.

The pituitary controls growth and development of the body tissues (the 'end organs') directly and via the thyroid, adrenals and gonads (the 'target glands') through the tropic hormones. The pituitary (the control centre) is itself controlled by the hypothalamic-hypophyseal nerve centres. Thus a disturbance in growth may be due to an upset in:

1. The nervous system;
2. The pituitary gland;
3. One of the target glands.

Though the growth factor can act directly upon the growth of body tissues it may be influenced by central nervous system lesions. In addition to a direct effect on growth the pituitary has a specific effect on the proliferation of cartilage and bone, and increases protein anabolism. Thyroxine has a marked influence upon growth and development, but it may only act as a catalyst for the pituitary growth factor.

Evans, Simpson and Pencharz[2] showed that hypophysectomy and thyroidectomy leads to cessation of growth. They found a synergism between thyroxine and the anterior pituitary growth-promoting substance, but thyroxine alone appeared to function only in intact animals as it did not work in hypophysectomized-thyroidectomized preparations. Talbot and Sobel[3] similarly found that human pituitary dwarfs did not respond to thyroid alone. Though Salmon[4] could not stimulate growth with pituitary extract in thyroidectomized animals, Scow and Marx[5] produced a definite increase in the weight of thyroidectomized rats with a purified growth hormone. Bone length was also increased but bone age was not advanced.

THE GONADS AND THE ADRENALS

During adolescence testicular androgens and ovarian oestrogens act as catalysts for epiphyseal maturation which, when complete, precludes further bone growth. Accelerated epiphyseal maturation may affect growth, since persons who mature early are shorter than those who mature late. Females mature 2 years before males, and their growth also ceases 2 years earlier. Besides influencing epiphyseal maturation, the androgens promote growth whereas oestrogens probably do not.

Eunuchoid subjects attain normal growth but do not continue to grow although the epiphyses are open. Hence epiphyseal maturation is not the only factor affecting the duration of growth during maturity. The cortico-adrenal androgens (17-ketosteroid precursors) are regarded as an accessory growth hormone during adolescence, in females as well. This is likely since females with hypoadreno-corticism maintain normal growth on salt and DOCA. Furthermore, urinary 17-

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ketosteroids increase during the latter half of adolescence, when the rate of growth steadily declines. This may be due to a diminished amount of pituitary growth factor at this time.

Recently methylandrostenediol, a steroid closely related to methyl testosterone, has been synthesized. It is active by mouth, does not produce masculinization in normal doses and utilizes dietary protein to maximum advantage. It can produce muscular growth in rats.[6] In children an effective response followed 20 mg. sublingually. The gain in weight was due not only to nitrogen but also to sodium and chloride retention.[7]

CASE NO. 1

J. V. S., an only child of 4 9/12 years (referred by Dr. F. H. Bachmann on 30 August 1951) had failed to gain since the age of 2 years. The mother (31 years), was well but the father (aged 34) suffered from rheumatoid arthritis. The pregnancy had been full term and the birth weight was 8 lb. 6 oz. He grew normally until the age of 2 years, walking at 18 months and talking at 30 months. In infancy he had frequent bouts of diarrhoea but was otherwise well.

Since the age of 2 he had virtually stopped growing. His appetite was poor because he was very constipated. He was not an active child. His skin was dry and he felt the cold badly. He was very bright mentally and knew his nursery rhymes at the age of 3. His fontanelle had not closed until he was 3.

He was very small for his age, with infantile facies and bodily proportions. The skin was dry but not coarse. The hair felt soft. Twenty teeth had erupted. The pulse rate was 100 per minute. The eyes and ears were normal. The throat was clear. The thyroid gland was not palpable. Heart and lungs appeared normal. The abdomen was protuberant, but no spleen or liver was palpable. The genitalia appeared normal for a 5-year old. The reflexes were normal.

Laboratory investigations on 25 August 1951 and 26 February 1952 revealed a slight hypochronic anaemia, with normal total and differential white cell counts, blood cholesterol, calcium, phosphorus and alkaline phosphatase.

The electrocardiogram was normal.

X-ray Findings (25 *August* 1951): The pituitary fossa was large, deep and rounded. The lumbar vertebrae were abnormally shaped and L2 was hook-shaped, as described in chondrodystrophy. The epiphyses of the femoral head were absent (usually present at 8 months). The bone age (according to Todd's *Atlas of the Wrist*) was between 3-6 months.

On 20 February 1952 the bone age was between 15 and 18 months. The femoral heads were present, showing marked epiphyseal dysgenesis.

Progress. The child was started on ½ gr. of thyroid daily, gradually increased to 3 gr. a day. In February 1952 his appetite had improved, he was alert and active and his bowels had become regular a month after the commencement of treatment. His abdomen had become markedly smaller and his skin was soft and warm. After 7 months of treatment the height increased from 35.5 to 38.5 inches. The weight was unchanged but the circumference of the abdomen decreased from 29 inches to 21 inches. In April 1953 (at the age of 6 5/12 years) his height was 42 inches. Eleven months later it was 45¼ inches, the weight being 50 lb. For the past year he had received thyroid gr. ii daily. His bone age was normal at this stage.

Comment. This 57-month-old child appeared to be a case of dwarfism with a bone age of 3-6 months. After 7 months on thyroid his bone age was 15-18 months. His growth had reached that of an average child of 3½ years. At 88 months his height was 45¼ inches and he had a normal bone age. This indicates a response of 9¾ inches in 31 months on thyroid treatment only.

CASE 2

An Indian girl aged 9 years 1 month was first seen in August 1951 because she had not grown for 4 years. The mother (aged 28) and the father (31 years) were both well. Three siblings (of 4 years, 2½ years and 6 months) were healthy. The 4-year-old was as tall as the patient. The pregnancy had been full term and the labour uncomplicated. The child's growth and development were perfectly normal. She walked at 15 months. Her first tooth erupted at 9 months. She had no previous illnesses. Her appetite was good and she ate a balanced diet including meat, fruit and vegetables. Her bowels were regular.

She was a slightly built child with infantile features and a warm but slightly coarse skin. Ears, nose and throat were normal. Twenty teeth had erupted. Heart and lungs were normal. The abdomen was slightly distended. The reflexes were present and equal. Cranial nerves were intact. The pituitary fossa was enlarged, mainly anterior-posteriorly, and to a lesser extent in depth. The lumbar spines showed some abnormality similar to that of a chondrodystrophy.

The wrist bone age was that of a 15-month-old child, and the epiphyses had not developed in the usual order. The femoral epiphyses were present, but showed marked dysgenesis. On 4 April 1952 the bone age was comparable to that of a 3½-year-old. The epiphyses of the femoral heads were now larger and the epiphyseal fragmentation was more marked.

Progress. She was started on thyroid in small doses, and gradually became more alert and active. The coarsening of the skin was absent in March 1952. The greatest change was in the growth. From an initial height of 37 inches she grew 3 inches in 7 months. As the growth appeared to have slowed somewhat she was treated with androgens and thyroid. In August 1953 (2 years after the institution of therapy) her height was 45 inches. Her PBI at this time was 1 microgram/100 ml. Her bone age was still markedly retarded. In May 1955 her height was 48 inches on the same therapy.

Comment. This child gained 11 inches in 44 months but part of her progress must be attributed to combined therapy of androgens and thyroid. As she has not returned to the normal range (as occurred in the first case) it is fair to presume that she has an additional absence of growth factor.

The differential diagnosis in these 2 cases depends upon the factors involved in growth and development. Wilkins[8] classifies them as follows:

CLASSIFICATION OF DWARFISM

1. *Bone Diseases*:
   - (*a*) Chondrodystrophies.
   - (*b*) All types of rickets.
   - (*c*) Osteogenesis imperfecta.
   - (*d*) Diseases of the spine.

2. *Nutritional or Metabolic Disorders*:
   (*a*) Coeliac disease and fibrocystic disease of the pancreas.
   (*b*) Chronic renal disease.
   (*c*) Hepatic insufficiency.
   (*d*) Nutritional defects and chronic infections.
3. *Circulatory Disorders and Anoxia*:
   (*a*) Congenital heart disease.
   (*b*) Extensive chronic pulmonary disease.
4. *Delayed Adolescence with Retarded Growth Spurt.*
5. *Primordial or Genetic Dwarfism*:
   (*a*) Familial.
   (*b*) Sporadic.
   (*c*) Syndrome of Ovarian Agenesis and Dwarfism.
6. *Unclassified Types*:
   (*a*) Progeria.
   (*b*) Dwarfism with severe brain defects.
7. *Endocrine Disturbances*:
   (*a*) Hypothyroidism.
   (*b*) Sexual precocity with early epiphyseal fusion.
   (*c*) Hypopituitarism.
   (*d*) Mixed types.

1. *Bone Diseases.* The chondrodystrophies are frequently mistaken for endocrinopathies. In the typical chondroplastic the dwarfism (genetically determined) is characterized by marked shortening of the limbs, especially the thighs and upper arms. The growing ends of the long bones are splayed out. The patient is lordotic and has a protuberant abdomen. The vertebrae and skull are usually normal. X-ray of the newborn is often diagnostic.

Morquio's disease (an atypical form in which the spine deformity suggests rickets) is not manifest before 1 year of age. The extremities are long in proportion to the spine and the epiphyseal ends may be fragmented, particularly in a rare type known as chondrodystrophia calcificans congenita, in which the epiphyseal centres of the long bones may show multiple foci of ossification (as in hypothyroidism). The vertebrae are often flattened and elongated, and superficially resemble cases of gargoylism, where the hook-shaped vertebral bodies follow defective development of a superior vertebral quadrant. The neural arches and bodies are also undeveloped. Other distinctive features in gargoylism are marked dwarfism, mental retardation, a large skull with an elongated flattened pituitary fossa, pot belly, coarse features, large tongue, hepatosplenomegaly and a cloudy cornea. The tubular bones are expanded in the mid-shaft region due to medullary infiltration of a granular material (glycogen and glycoprotein). The ends of bones are narrowed and epiphyses are not involved. An X-ray diagnosis cannot be made before 6 months of age, although the clinical features may be suggestive almost from birth.[9]

In achondroplastics and Morquio's disease there is a paucity of metaphyseal change, the chief features being a diaphyseal expansion. All blood chemistry is normal in these conditions. Rickets of the classical type is not usually mistaken for dwarfism, but certain cases of vitamin D-refractory rickets and rickets due to renal disturbances, e.g. the Fanconi syndrome, may present as dwarfism.

Osteogenesis imperfecta is due to an inferiority of the mesenchyme resulting in multiple fractures which may be present at birth. The bone cortex is thin and multiple deformities due to fractures may be seen.

Tuberculous involvement of the spine, resulting in collapsed vertebrae with usually marked kyphosis, may also cause dwarfism.

2. *Nutritional or Metabolic Disorders.* These are easily diagnosed. They are all due to inadequate intake, absorption or utilization of food. Many cases of dwarfism are due to caloric inadequacy.[3] Protein is very important provided the anabolic hormone supply is enough. Lack of protein may depress the growth hormone and lead to a so-called secondary hypopituitarism. In certain conditions, e.g. coeliac disease or impaired hepatic function, a diminished mineral intake may result in a type of rickets. Any chronic infection produces dwarfism through inadequate food intake and excessive breakdown of protein tissues.

3. *Circulatory Disorders and Anoxia.* Congenital heart disease and chronic lung infections retard development by poor oxygenation of the tissues. The cyanotic cases of congenital heart disease cause the most marked growth disturbance.

4. *Delayed Adolescence with Retarded Growth Spurt.* This is usually seen at puberty when there is a failure of the normal spurt in growth and sexual development. There is no defect but only a delay in the activation of the pituitary-gonad-adrenal system. The bone age (X-ray) is within normal limits.

5. *Primordial Dwarfism.* This may be genetically determined (as in certain pygmies) although a few cases may be sporadic in onset. The bone age and the mentality are within normal limits. These children are usually small at birth. In so-called ovarian agenesis and dwarfism the ovarian deficiency does not appear to be a factor, since öophorectomy does not produce dwarfism. The pattern of growth and development resembles that of the primordial dwarf. The epiphyseal ossification is

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only slightly delayed, if at all. These patients do not have the childlike facies of hypopituitary dwarfs. In fact, they often resemble one another, with rather mature features and poorly developed jaw and chin. Other defects such as webbed neck, coarctation of the aorta and eye defects may be present.

6. *Unclassified Types.* Progeria is a type for which no definite cause can be assigned. All the cases are alike. There is no familial incidence. At birth they are normal. They cease to grow from a few months to 3 years. The features become shrunken and drawn, the nose thin and beak-like. The hair and subcutaneous tissue may be lost completely. The epiphyses often fuse early and premature death follows arteriosclerosis. Atypical forms have also been described. The literature is briefly reviewed by Thomson and Farfar.[10]

7. *Endocrine Disturbances.* Sexual precocity due to excessive androgen leads to an early rate of growth and development, but premature epiphyseal fusion causes early cessation of growth and consequent dwarfism. The so-called mixed type of endocrine dysfunction should only be diagnosed when more definite specific endocrine tests become available.

Hypothyroidism and hypopituitarism (the 2 most important endocrinopathies) are in many ways very similar, but they can be differentiated by appropriate tests.

It may be difficult to exclude pituitary dwarfism from hypothyroidism. Evidence of pituitary tumour or change in the pituitary fossa is very rare. The hypopituitary dwarfs are usually normal at birth. Their growth in infancy depends on an intrinsic growth tendency of the tissues. Cessation of growth usually occurs by 2 or 3 years of age. The children have normal growth proportions for their age, unlike hypothyroid cases. The face is more mature and the expression alert. The skin is warm and soft and the circulation is normal. A marked retardation in bone age is frequently present. The frequently elevated blood cholesterol makes the diagnosis more difficult.

A definite and significant feature is (according to all authorities), the absence of epiphyseal dysgenesis. These cases are insulin-sensitive and may have hypoglycaemic attacks. Urinary 17-ketosteroids are low, as is the follicle stimulating hormone (FSH) which is diminished to below 6 mouse units per day.

These children also fail to mature sexually. At 20–30 years they show definite ageing and drying of the skin. A therapeutic test with thyroid may be diagnostic. Thorn and his co-workers[11] regard epinephrine as diagnostic, since it should fail to evoke an eosinophil response in hypopituitarism.

Hypothyroidism is the most common endocrine cause of dwarfism.[8] The first type (present since birth) may be sporadic or endemic. The second (so-called juvenile) type can be divided into 4 groups. By far the largest group is of unknown cause. The others can be attributed to thyroiditis, operative removal or are secondary to pituitary deficiency. Those affected since birth often have characteristic coarse features which may be noticeable at a few weeks of age. In the juvenile types the characteristic facies is absent and the only manifestations may be retarded growth and development, i.e. dwarfism. The structural change is stunted growth, in which the proportions are infantile. Engelbach[12] reports the ratio of upper to lower segment at birth as 1.7 : 1. The lower segment is measured from the top of the symphysis pubis to the soles.

Because the lower segment grows more rapidly, at 5 years the ratio is 1.2 and at 10–12 years it is 1.1. Osseous development is markedly retarded and epiphyseal dysgenesis is almost always present. Dental development is retarded and may be defective. Two features which are not well described in the literature, but are mentioned by British authors, is an enlarged pituitary fossa which is present in the 2 cases here described. The characteristic naso-labial configuration in hypothyroidism is due to the flat, broad nasal bridge, causing the eyes to appear widely spaced. The nose itself is short and underdeveloped. This abnormality is due to failure of growth at the sphenoccipital bones.[13] Dye and Maughan[14] have shown that endochondral bone is retarded in hypothyroidism but not membranous bone.

The most characteristic almost specific skeletal change in hypothyroidism is epiphyseal dysgenesis, due to a disorder of epiphyseal cartilage of round bones leading to irregularities in their subsequent ossification. It is usually most marked in the femoral head but can involve all the endochondral centres in which ossification normally occurs during the deficiency state. Wilkins[8] found this sign present in all but 2 of 25 cases. In these 2 the X-rays were only taken long after the treatment began. This finding is occasionally more marked after therapy is instituted. Two other conditions which may be confused are Perthes' disease and chondrodystrophy.

The vertebral changes reported here (and most marked in 12) also occur in cretins.

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This finding is well described by Swoboda[15] in 7 cases of congenital myxoedema. The findings are very similar in all cases and consist of blunting of the upper border of the vertebrae. This constant sign is usually missed as it is mild in most cases, and the kyphosis is usually attributed to the muscular hypotonicity of hypothyroidism. Similar findings occur in gargoylism and Morquio's chondrodystrophy. Caffey[9] attributes vertebral displacement of the thoracic and lumbar vertebrae to retarded development and hypoplasia of the articular processes. According to British authors, a band of increased density at the end of long bones resembling that of lead poisoning can be seen, but this was not noted in the 2 cases quoted.

Topper[16] discusses mental development in hypothyroidism. He concludes that there is no correlation between adequate therapy and mental retardation. Electroencephalographic evidence suggests that the lack of mental development is an associated cerebral defect which cannot be modified by therapy. In the cases of N. M. and J. V. S. the intelligence appears to be normal. As N. M. is of Indian descent, no suitable intelligence tests could be used, while J. V. S. on superficial testing appeared to be normal for a 5-year-old before therapy was instituted. In a doubtful case an EEG may be of prognostic value.

Certain fundamental changes which may be present are marked mental and physical inactivity (to be distinguished from mental retardation). The circulation is usually sluggish and the extremities cold. These children have marked constipation due to atony of the gut wall. This lack of muscular tone causes marked abdominal distension (as in the case of J. V. S.) before and after treatment. The constipation may at times alternate with diarrhoea, which is attributed to myxoedematous infiltration of the bowel wall.

For diagnostic confirmation certain tests have proved helpful. A simple one is the blood cholesterol level which, in hypothyroidism, varies between 250 and 600 mg. per 100 c.c. (normal value: 100–300 mg. per 100 c.c.). In a hypothyroid, however, the level may fluctuate more than 200 mg. per 100 c.c. in a single case, while in a normal this fluctuation is much less. Wilkins[8] found that a 2 mg. (intramuscular) injection of thyroxine reduces the cholesterol level in a hypothyroid patient for an average period of 40 days, instead of 10 days in control cases.

A further diagnostic test is the withdrawal of thyroid therapy in a doubtful case, when the blood cholesterol (after 8 to 12 weeks) may show a marked rise. A similar rise does not occur in other types of dwarfism.

A very valuable test in adults is the BMR. In infants and children it is not satisfactory. Should it be done, however, the result should be compared with the height-weight standards of Talbot in preference to the surface area method of Boothby-Sandiford.

Robertson and Kirkpatrick[17] agree with other authors that in cases of hypothyroidism the protein-bound-iodine (PBI) level is below 4 micrograms per 100 c.c. and that this is a valuable and more accurate test for following the adequacy of therapy. The PBI falls very rapidly and is usually stabilized within 2 weeks. In the case of the BMR, stabilization does not develop for at least 4 weeks. As the BMR is not accurate in children, the PBI would be a better procedure.

A very valuable test is the thyroid uptake and urine excretion of I 131. Reilly and Bayer[18] have used small doses (5 microcuries in children under 6 and 10 microcuries over 6). In normal children the thyroid uptake was 8.7–29.8% in 24 hours and the urinary excretion was 54.7% in 96 hours. In congenitally hypothyroid patients the uptake was 1–2%, and was not affected by thyroid medication. The urinary excretion for 96 hours was 73.5–92.4%.

A new test (still in the experimental stage but possibly valuable in cases of dwarfism) is the use of lyophilized thyrotrophic hormone (TSA) to distinguish between primary hypothyroidism and primary hypopituitarism After a TSH injection, estimating the PBI, the iodine uptake of the thyroid or the blood cholesterol are measured. Querido and Stanbury[19] gave 12.5 mg. TSA twice a day.

Other tests which have proved of slight value are the urinary excretion of creatine-creatinine, blood phosphorus levels and the electro-cardiographic findings. Braid,[20] however, feels that EGG changes are more specific than X-ray of the heart, the characteristic features being a low voltage curve with flat P and T waves. The P-R interval is usually normal. Table 1 summarizes helpful data.

Despite all the tests, the response to thyroid may be diagnostic. This can be checked simply by measurements of the bone age. One can predict a growth of 6–9 inches in the first year.[21] The following year it will drop to 4 inches even when the dose is doubled. In the third year the gain will only be a normal rise. Should the response not be satisfactory, testosterone can be given in addition. Examilla

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TABLE I

	Juvenile Hypothyroidism	*Pituitary Dwarfism*
Infantile Proportions	Yes	No
Bone Age	Markedly Retarded	Marked to slight
Epiphyseal Dysgenesis	Majority	Occasionally
Pituitary Enlargement	Frequently	Occasionally
Vertebral Changes	Often	Occasionally
Blood Cholesterol	Raised	Usually normal
Response to Epinephrine	Positive	Absent
Response to TSH	Usually absent	Positive

and Bennett[22] treated a so-called case of pituitary dwarfism with purified growth hormone without any result. Testosterone and thyroid were ineffective separately but when given together the effect was pronounced. This suggests that thyroxine and testosterone may have a synergistic action. Methylandrostenediol can be used in place of testosterone.

CONCLUSIONS

After prolonged treatment it was observed that the first case continued within normal limits on thyroid alone. It can be considered a true case of hypothyroidism.

In the second case, however, it is seen that adequate growth was not maintained even on androgens and thyroid and perhaps this case is more truly one of pituitary insufficiency. This may also suggest that epiphyseal dysgenesis may occur in dwarfism of pituitary origin, although it may be due to thyrotropic hormone deficiency.

A definite case of pure thyroid deficiency can only be confirmed after a minimum period of 2 years on therapy.

SUMMARY

The various factors involved in growth and development are reviewed briefly.

Two cases of dwarfism are considered with reference to their X-ray findings and response to therapy.

A classification of dwarfism is outlined and the various types considered.

The 2 types which may be difficult to assess are those of hypopituitarism and hypothyroidism.

Special features are noted and various tests reviewed.

It appears, however, that the final diagnosis may ultimately depend on the prolonged effect of thyroid medication.

OPSOMMING

Die verskillende faktore wat 'n invloed op groei en ontwikkeling uitoefen, word kortliks hersien.

Twee gevalle van dwergisme word oorweeg in die lig van die X-straal-bevindings en hul reaksie op terapie.

'n Klassifikasie van dwergisme word geskets, en die verskillende tipes word oorweeg.

Die 2 tipes wat waarskynlik moeilik sal wees om te diagnoseer, is hipopituïtarisme en hipotiroïdisme.

Daar word gelet op spesiale kenmerke, en 'n oorsig word verstrek van verskillende toetse.

Dit skyn, egter, asof diagnose in die finale instansie van die langdurige effek van skildklierbehandeling sal afhang.

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PREPARATE EN TOESTELLE

CHLOROMYCETIN-HIDROKORTISOON-OFTALMIES

P. D. & Co. (Pty.) Ltd., die Suid-Afrikaanse filiaalmaatskappy van Parke Davis & Co., kondig die beskikbaarstelling aan van 'n antibioticum-hormoonsamestelling vir plaaslike aanwending in gevalle van infeksies van die oog—Chloromycetin-hidrokortisoon-Oftalmies.

Die uitgebreide bakterie-bestrydende bedrywigheid van Chloromycetin maak dit 'n antibioticum wat veral geskik is vir die behandeling van ooginfeksies, terwyl die kleinheid van die Chloromycetin-molekule dit in staat stel om maklik tot die dieper weefsels van die oog deur te dring. Die goeie hoedanighede van hidrokortisoon by die behandeling van ontstekingstoestande van die oog, is welbekend. Die terapeutiese effek van hidrokortisoon word uitgeoefen op al die lae van die oog, met die gevolg dat pyn en fotofobie aanmerklik verlig word. Die gevaar dat nuwe bloedvate oor die deursigtige media van die oog gevorm sal word, word aansienlik verminder, en die vernietigende en ongeneesbare gevolge van ernstige oogontsteking word dikwels voorkom. Chloromycetin-Hidrokortisoon-Oftalmies is dus 'n besonder doeltreffende samestelling by die behandeling van akute en kroniese infeksies van die oog, aangesien die infeksie vinnig deur die Chloromycetin-bestanddeel gekontroleer word, terwyl die hidrokortisoon vinnige genesing met minimum-littekenweefsel-vorming in die hand werk.

Indikasies: (1) Akute ontstekingsiektes van die voorste segment, soos reënboogvliesontsteking, keratoconjunctivitis gepaard met horingvliessweertjies, randstandige swere, die bulbêre vorm van lenteconjunctivitis, en aangebore sifilitiese keratitis.

(2) Infeksies van die buite-oog en adnexa veroorsaak òf deur *Micrococcus pyogenes* var. *aureus*, betahemolitiese streptokokki, pneumokokki, *Escherichia coli*, *Haemophilus influenzae* òf *Moraxella lacunata*.

(3) Traumatiese letsels van die oog.

Gebruiksaanwysings: Chloromycetin-Hidrokortisoon-Oftalmies word vir gebruik voorberei deur 5 k.s. steriele gedistilleerde water by die inhoud van die flessie te voeg onder aseptiese toestande, en dit dan te skud totdat dit 'n eenvormige suspensie vorm. Die dosis is wisselbaar, en hang af van die oordeel van die geneesheer wat die erns van die infeksie, die diagnose, die duur van die infeksie vóór behandeling, en die reaksie van die pasiënt in aanmerking moet neem. Die volgende behandeling word aanbeveel:

1. Gedurende die eerste 24–48 uur: Twee druppels in die aangetaste oog, elke 1–3 uur, nag en dag.

2. Ná 24–48 uur: Twee druppels elke 3–4 uur gedurende die dag. Nag-indrupping kan, indien verlang, oorgeslaan word. Gaan voort totdat die oog 48 uur lank normaal is.

Die behandeling met Chloromycetin-Hidrokortisoon-Oftalmies moet nie skielik gestaak word nie. 'n Herhaling van die kwaal is waarskynliker wanneer die terapie skielik stopgesit word as wanneer dit geleidelik tot 'n einde gebring word. Indien daar 'n herhaling voorkom, moet die geneesheer die behandeling wat hierbo beskryf is weer van vooraf begin.

Inligting oor Verpakking: Flessies van 5 k.s. met 'n druppelaar. Iedere flessie bevat, in droë vorm, 12.5 mg. Chloromycetin en 25 mg. Hidrokortisoon asetaat met Boraatbuffer vir die voorbereiding van 5 k.s. sweefmengsel deur die byvoeging van steriele, gesteriliseerde water voor gebruik.

KARMOPLEX: HYPEREMESIS GRAVIDARUM

Petersen Beperk van Barrackstraat, Kaapstad, is bly om 'n toevoeging tot hulle reeks van etiese produkte aan te kondig.

Hierdie preparaat, Karmoplex, word aan die mediese beroep aangebied as 'n middel om die kommervolle toestand van hyperemesis gravidarum te bestry. Karmoplex bevat Piridoxine-hidrochloried—25 mg. asook 0.25 gram Fenobarbitoon. Te wyte aan die hoër Piridoxine inhoud, sowel as die Fenobarbitoon in die suiker omhulsel van die tablet, word onmiddellike verligting verkry deur pasiënte wat ly aan mislikheid.

Karmoplex tablette word verpak in bottels van 20, 60 en 250 tablette elk.

DEXEDRINE PLUS

'Dexedrine Plus' is bedoel vir die behandeling van vetsug veral by pasiënte soos kinders en swanger vrouens by wie die instandhouding van 'n voldoende voorraad vitamines en minerale noodsaaklik is. In 'n enkele kapsule bied dit 'n normale dosis 'Dexedrine' en 'n hoeveelheid—genoegsaam om aan voedingsbehoeftes te voldoen—van die essensiële vitamines en minerale wat miskien in 'n lae-kalorie-diëet ontbreek.

Dosis en Toediening. Die gewone dosis 'Dexedrine Plus' is 1 kapsule drie maal per dag, 30 tot 60 minute *voor* maaltye. In die geval van sommige pasiënte sal groter dosisse miskien nodig wees. As die pasiënt 'n ligte slaper is, moet die laaste dosis van die dag so vroeg toegedien word dat dit nie die nagrus versteur nie.

Spesiale Oorwegings. 'Dexedrine Plus' moet versigtig gebruik word in die geval van pasiënte wat oormatig gevoelig is simpatomimetiese samestellings; in gevalle van koronêre of kardiovaskulêre kwale waar daar 'n kontra-indikasie van vasokonstriktors is; en in gevalle waar daar opvallende hipertensie is. Hiperopgewondenheid en verontruste prepsigotiese toestande is kontra-indikasies vir sover dit die gebruik van hierdie middel betref.

Formule. Iedere 'Dexedrine Plus'-kapsule bevat:

Dextro-amfetamine-sulfaat ('Dexedrine')	5 mg.
Dikalsium-fosfaat, U.S.P.	250 mg.
Aneurine-hidrochloried	0.4 mg.
Riboflavine	0.6 mg.
Nikotinamied	4 mg.
Ferr. Sulph. Exsic.	13.4 mg.
Vitamine A	1,680 eenhede
Vitamine D	500 eenhede

Verpakking. 'Dexedrine Plus' is verkrygbaar in bottels bevattende 50 kapsules.

IMFERON (BINNESPIERSE YSTERINSPUITING)

Imferon is 'n oplossing van 'n yster-dextran-kompleks. Iedere millilieter verskaf die ekwivalent van 50 mg. elementale yster.

Indikasies. Bloedarmoede tydens swangerskap; versteurde absorpsie van yster; ondoeltreffende mondelinge dosisse; diëettekortkominge; kroniese bloedverlies; ondervoeding; kroniese infeksies; ontstekingstoestande en hartkwale gepaard met 'n lae hemoglobine-peil.

Dosis. (*a*) Hemoglobine uitgedruk as 'n per-

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sentasie. Die volgende formule dui die hoeveelheid Imferon aan wat nodig is om die hemoglobinekonsentrasie tot normaal te herstel. W = die pasiënt se gewig in ponde, en Hb% = die waargenome hemoglobine.

$$\frac{0.3\ W\ (100 - Hb\%)\ \text{ml.}}{50}$$

Voorbeeld. 'n Pasiënt weeg 125 pond en het 'n hemoglobine van 60%. Die formule word dan

$$\frac{0.3 \times 125 \times (100 - 60)\ \text{ml.}}{50} = 30\ \text{ml.}$$

(*b*) Hemoglobine uitgedruk as gram per 100 ml.

Die formule is $\frac{1.3\ W\ (19 - Hb)\ \text{ml.}}{50}$

Voorbeeld. 'n Pasiënt weeg 100 pond, en het 'n hemoglobine van 9.0 G./100 ml.

Die formule word dan

$$\frac{1.3 \times 100 \times (19 - 9)\ \text{ml.}}{50} = 26\ \text{ml.}$$

In die geval van kinders is die maksimum-dosis: swaarder as 20 pond, nie meer as 2 ml. nie; swaarder as 8 pond, nie meer as 1 ml. nie; ligter as 8 pond, nie meer as 0.5 ml. nie.

Toediening. Imferon moet diep in die boonste buite-kwadrant van die boud of die laterale sy van die dy ingespuit word. Gebruik 'n 20 s.w.g.-naald van 2 duim.

Verpakking. Ampulle van 2 ml., bevattende die ekwivalent van 100 mg. elementale yster, word in hoeveelhede van 10 en 100 verpak. Ampulle van 5 ml., bevattende die ekwivalent van 250 mg. elementale yster, word in hoeveelhede van 5 en 50 verpak.

Verspreiders. Fisons Chemicals (S.A.) (Pty.) Ltd., Commissionerstraat 259, Johannesburg.

OXSORALEN EN VITILIGO

Oxsoralen (Elder)-merk metoxsalen is 'n samestelling (8-metoxypsoralen) wat van plantaardige bronne geïsoleer is, en by die behandeling van vitiligo gebruik word.

Die inwoners van Egipte, Indië en, in 'n geringer mate, ook ander lande, het talle eeue lank geprobeer om vitiligo met die uittreksels van sekere plante te behandel. Hierdie stowwe (wat help met die produksie van melanine-pigment) word aangetref in etlike plante, insluitende *Fagara xanthoxtloides* en *Ammi majus* Linn.[1-4]

Formulering. Oxsoralen vir mondelinge terapie: in vleeskleurige kapsules bevattende 10 mg. 8-metoxypsoralen.

Vir plaaslike behandeling is dit verkrygbaar as 'n helder asetoon- alkohol-, propileen-, glikol-middel, bevattende 1% van 8-metoxypsoralen.

Indikasies. Oxsoralen word mondeling, in kombinasie (d.w.s. mondeling sowel as plaaslik), of plaaslik gebruik vir die behandeling van idiopatiese vitiligo. Volledige besonderhede oor die behandelingsmetodes is van die verspreiders verkrygbaar.

Kontra-indikasies. Oxsoralen moet nie geneem word as daar aanduidings van lewerverswakking of suikersiekte is nie.

Lewerfunksie-toetse moet maandeliks gedurende die eerste 3 maande uitgevoer word, en dan minder dikwels solank die behandeling voortduur.

Oxsoralen het geen uitwerking op die leukoderma geassosieer met die vernietiging van melanosiete wat ná ernstige brandwonde en trauma voorkom nie. Sover bekend, het dit ook geen uitwerking op die leukoderma wat op infeksies soos pinta of leprose volg nie.

Verspreiders: Protea Pharmaceuticals, Ltd., Posbus 7793, Johannesburg.

VERWYSINGS

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FLORINEF MET GRANEODIN

SALF OF LOTIO VIR ONTSTEKINGS- EN ALLERGIESE VELKWALE

Beskrywing: *Florinef met Graneodin* verenig die ontstekings- en jeukbestrydende effek van Florinef (Squibb se Fluorohidrokortisoon-asetaat) met die bakteriebestrydende effek van Graneodin (Squibb se Neomisine-Gramasidine).

Die *Salf* is 0.1% fluorohidrokortisoon-asetaat verenig met 2.5 mg. neomisine en 0.25 mg. gramisidine per gm. plastikabasis (Squibb se Olierige Salfbasis wat geen water absorbeer nie). Die *Lotio* is 0.1% fluorohidrokortisoon-asetaat verenig met 2.5 mg. neomisine en 0.25 mg. gramisidine per ml. waterverdunningsmiddel.

Uitwerking: Florinef is 'n jeukbestryder, en voorkom ontstekingsreaksies op bakteriese, allergeniese en ander skeikundige middels. In baie gevalle is dit 25 keer sterker as hidrokortisoon.

Neomisine *in vitro* is doeltreffend teen 'n verskeidenheid van Gram-negatiewe en Gram-positiewe organismes. Gramisidine is doeltreffend *in vitro* teen Gram-positiewe organismes, maar het min uitwerking op Gram-negatiewe organismes. *Strep. haemolyticus* wat weerstandskragtig is vir sover dit neomisine betref, is hoogs vatbaar vir gramisidine. Die organismes wat geassosieer is met die merendeel van die oppervlakkige infeksies van die vel word òf vernietig òf gestrem deur neomisine-gramisidine.

Voordele: *Florinef met Graneodin* verenig die kragtige ontstekings- en jeukbestrydende terapie van fluorokortisoon met die profilaktiese effek van neomisine-gramisidine, en beskerm die pasiënt derhalwe teen sekondêre infeksie.

Dit is doeltreffend in die geval van baie pasiënte wat net effens, of glad nie reageer nie op die plaaslike aanwending van hidrokortisoon.

Weens sy breë bakteriebestrydende spektrum verminder Graneodin die gevaar van 'n sekondêre siekte-inval.

Sensitisasie vir sover dit *Graneodin* betref, is 'n seldsame verskynsel. As dit wel voorkom, verhinder die plaaslike aanwending van *Graneodin* nie die latere gebruik van mondelinge of parenterale antiobiotica nie.

Indikasies: *Florinef met Graneodin* word aanbeveel vir die behandeling van nie-aansteeklike velkwale wat reageer op die plaaslike aanwending van hidrokortisoon of op Florinef-terapie. Huidontsteking (atopiese, eksematoïde, kontak—insluitende

giftige klimop); huidontsteking van die hande; neurodermatitis; lichen simplex chronicus; ekseem (atopies, dishidroties, stasies, muntvormig); kinder-ekseem; anogenitale pruritus; sonbrand.

Dit is veral nuttig teen sekondêre infeksies.

Toediening: *Florinef met Graneodin* word 2 tot 4 maal per dag baie liggies aan die aangetaste dele gewend. Aanwending oor groot oppervlaktes gee aanleiding tot perkutane absorpsie.

Bykomstige Effekte: Natrium-retensie met edeem is in uitsonderlike gevalle berig ná die gebruik van fluorokortisoon. As edeem voorkom, moet die behandeling tydelik gestaak word. Kaliumchloried, 3 gm. per dag, en 'n beperking van die natrium in die diëet, kan die verdwyning van die edeem bespoedig.

Verpakking: *Salf*, opvoubare buisies wat 5 gm. bevat; *Lotio*, plastiese drukbotteltjies met 15 k.s.

Verspreiders: Protea Pharmaceuticals Ltd., Posbus 7793, Johannesburg.

MYCOSTATIN (SQUIBB MYSTATIN)

Beskrywing: Mycostatin (ontleen aan die kwekings van *Streptomyces noursei*) word aanbeveel vir die voorkoming en behandeling van die ingewands-moniliase wat met die mondelinge toediening van antibiotica geassosieer is.

Fisiese Eienskappe: Kristalvormige Mycostatin is 'n liggeel, byna kleurlose stof. Die empiriese formule is $C_{47}H_{73}NO_{18}$. Dis aansienlik minder oplosbaar as onsuiwere materiaal, en is betreklik stabiel solank dit droog gehou word. Waar water egter aanwesig is, breek dit vinnig op.

Swambestrydende aktiwiteit, in vitro: Dit strem die ontwikkeling van, of vernietig alle soorte swamme en suurdeeg waarop dit getoets is, met die uitsondering van die aktinomisete. Dit oefen sy grootste effek uit op suurdeeg-agtige swamme in die groeistadium; dis minder aktief in die geval van spore, en onaktief teen bakterieë.

Absorpsie en Ontlasting: Mycostatin word swak *per os* geabsorbeer; onbenullige hoeveelhede verskyn in die bloed, maar aansienlike hoeveelhede in die ontlasting.

Giftigheid: Feitlik nie-giftig *per os*. Pasiënte het mondelinge dosisse van soveel as 6 miljoen eenhede per dag 'n hele paar maande lank verdra sonder sistemiese vergiftiging of sensitisasie, hoewel groter dosisse mislikheid, braking of diarree in 'n paar gevalle veroorsaak het. Dit is nie altyd moontlik om die bykomstige effek van Mycostatin te onderskei van dié van chloortetrasikline wat gelyktydig toegedien word nie. Volgens een verslag het 5.4 miljoen eenhede per dag geen bykomstige effek gehad nie. Maar braking het plaasgevind toe twee keer soveel toegedien is.

Indikasies: Die tablette word voorgeskryf vir die teenwerking van ingewandswamme en -suurdeeg-soorte, veral by pasiënte wat langdurige mondelinge behandeling ondergaan met antibiotica wat aktief teen ingewandsbakterieë optree.

Pasiënte wat met behulp van mondelinge antibiotica vir ingewandschirurgie voorberei word, moet ook met Mycostatin beskerm word.

Dit word aanbeveel vir die behandeling van pasiënte wat bewys lewer van tussenkomende infeksie met ingewandswamme.

'n Aansienlike aantal pasiënte wat antibiotica per mond kry, sonder die volledige beeld van kliniese moniliase, ly aan ingewandsontsteking en diarree, wat soms gepaard gaan met verswering en anus-fissuur. Ingewandsmoniliase kan die voorloper van 'n algemene infeksie wees. Sodanige ontwikkelinge kan egter met behulp van Mycostatin voorkom word; gevestigde moniliale infeksie van die ingewande word binne 24-48 uur deur die middel teëgewerk.

Dosis: Een 500,000-eenheid-tablet, 3 maal per dag, per mond. As die swamme nie behoorlik teëgewerk word nie, kan die dosis verdubbel word. Mycostatin kan saam met al die mondelinge antibiotica in gewone gebruik toegedien word, en behandeling daarmee moet voortduur ten minste net so lank soos die behandeling met die bakteriebestrydende middel. Dis miskien ook raadsaam om die Mycostatin-behandeling 'n rukkie langer voort te sit.

Verpakking: 500,000-eenheid-tablette, bottels van 12 en 100.

Verspreiders: Protea Pharmaceuticals Ltd., Posbus 7793, Johannesburg.

PENTOXYLON

Pentoxylon verteenwoordig 'n heeltemal nuwe benadering van die vraagstuk van angina pectoris; dit wil sê, dit is toegespits op die verligting van die koronêre kramp sowel as die verbanning van die angs van die pasiënt wat in doodse vrees vir die volgende aanval verkeer. Heeltemal tereg word dit ‚diepte-terapie' genoem, en die oogmerke daarvan is die vermindering van die nitrogliserine-behoeftes, die voorkoming of verligting van angina-aanvalle, en die verbanning van die psigiese spanning voortvloeiende uit vrees en gedurige angs.

Iedere langwerkende tablet bevat 10 mg. pentaeritritol-tetranitraat en 1 mg. rauwiloïde.

Kliniese proefnemings het bewys dat Pentoxylon goed verdra word. Die skadelike bywerkinge is van 'n geringe aard en kom slegs in uitsonderlike gevalle voor. Selfs hoofpyn het in nie meer as 10% van die gevalle voorgekom nie, en is maklik met behulp van asperine verlig sonder dat dit nodig was om die behandeling met die middel te staak. Geen toleransie het ontwikkel nie.

Meer as twee weke van terapie is nodig vir die ontwikkeling van die volle doeltreffendheid van Pentoxylon, hoewel merkbare voordele gewoonlik na 24 tot 48 uur waargeneem kan word.

Die gewone dosis is een tablet q.i.d., maar twee keer soveel is soms wenslik en kan goed verdra word.

Die enigste moontlike kontra-indikasie is glaukoom, maar onlangse proefnemings het twyfel selfs hieroor laat ontstaan.

Pentoxylon is verkrygbaar deur die gewone kanale in houers wat 25 en 100 tablette bevat. Dit word vervaardig deur Riker Laboratories Africa (Pty.) Ltd., Posbus 1355, Port Elizabeth, wat u met genoeë van leesstof sowel as materiaal oor kliniese proefnemings sal voorsien.

MONDELINGE BICILLIN

Wyethical (Pty.) Ltd. kondig die beskikbaarstelling aan van 'n nuwe variant van mondelinge Bicillin (Bensatien-penisilline G) in die vorm van pediatriese druppels, ideaal vir die behandeling van die gewone infeksies by suigelinge wat deur penisilline-sensitiewe organismes veroorsaak word.

Hierdie nuwe dosisvorm van Bicillin is so hoog gekonsentreer en so heerlik gegeur dat dit aan suigelinge toegedien kan word sonder dat hulle gekon-

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disioneer word om hul formule- of ander voedings te weier, soos so dikwels gebeur wanneer antibiotica saam met hul voeding aan hulle gegee word. Temeer, moeders hoef hulle nie te bekommer om iedere dosis medisyne saam met die voeding in die kind in te kry nie, want Bicillin-druppels, net soos die ander mondelinge vorms van Bicillin, bied gewisse weerstand teen maagdegradasie. Bicillin-druppels kan derhalwe vóór, ná of met die voeding toegedien word.

Iedere kubieke sentimeter van hierdie stabiele en smaaklike sweefmengsel verskaf 150,000 eenhede Bicillin. Die druppelaar is gekalibreer om 100,000 eenhede—'n gerieflike, pediatriese dosissterkte—te lewer.

Verpak in bottels wat 10 k.s. bevat.

PREPARATIONS AND APPLIANCES

CHLOROMYCETIN-HYDROCORTISONE OPHTHALMIC

P. D. & Co. (Pty.) Ltd., the South African subsidiary of Parke, Davis and Company, announce the introduction of an antibiotic-hormone combination for topical application in infections of the eye—Chloromycetin-Hydrocortisone Ophthalmic.

The wide antibacterial activity of Chloromycetin makes this an antibiotic particularly suited to the treatment of ophthalmic infections, whilst the small size of the Chloromycetin molecule enables it to penetrate the deep tissues of the eye readily. The advantages of hydrocortisone in the treatment of inflammatory conditions of the eye are well known, the therapeutic action of hydrocortisone being exerted through all layers of the eye with the result that pain and photophobia are noticeably relieved. The danger of new blood vessels forming across the transparent media of the eye is markedly reduced, and the destructive and irreversible consequences of severe eye inflammations are often prevented. Thus Chloromycetin-Hydrocortisone Ophthalmic is a particularly effective combination in treating acute and chronic infective conditions of the eye, as the infection is rapidly controlled by the Chloromycetin component whilst the hydrocortisone promotes rapid healing with a minimum formation of scar tissue.

Indications: (1) Acute inflammatory diseases of the anterior segment such as iritis, phlyctenular keratoconjunctivitis, marginal ulcer, bulbar form of vernal conjunctivitis and congenital syphilitic keratitis.

(2) Infections of the outer eye and adnexa caused by either *Micrococcus pyogenes* var. *aureus*, beta haemolytic streptococci, pneumococci, *Escherichia coli, Haemophilus influenzae* or *Moraxella lacunata.*

(3) Traumatic lesions of the eye.

Usage: Chloromycetin-Hydrocortisone Ophthalmic is prepared for use by adding 5 c.c. sterile distilled water to the contents of the vial under aseptic conditions and shaken to make a uniform suspension. The dosage is variable and depends upon the judgment of the physician, who must consider the severity of the infection, diagnosis, duration of infection before treatment and the response of the patient. The suggested treatment schedule is as follows:

1. First 24–48 hours: Two drops to the affected eye every 1–3 hours night and day.

2. After 24–48 hours: Two drops every 3–4 hours during the day, night instillations being omitted if desired. Continue until the eye has appeared normal for 48 hours.

Treatment with Chloromycetin-Hydrocortisone Ophthalmic should not be stopped abruptly since relapse is more likely to occur on sudden cessation of therapy than when tapered slowly to conclusion. Should relapse occur, the schedule of treatment outlined above should be restarted.

Package Information: Vials of 5 c.c. with a dropper, each vial containing in dry form 12.5 mg. Chloromycetin and 25 mg. Hydrocortisone Acetate with Borate Buffer for the preparation of 5 c.c. of suspension by adding sterile distilled water before use.

KARMOPLEX: HYPEREMESIS GRAVIDARUM

Petersen Limited of Barrack Street, Cape Town, announce Karmoplex as an addition to their range of ethical products. This preparation is offered to the medical profession as a means of overcoming the distressing condition of hyperemesis gravidarum.

Karmoplex contains Pyridoxine Hydrochloride—25 mg. and Phenobarbitone 0.25 gram. Due to the higher Pyridoxine content, and also since the Phenobarbitone is embodied in the sugar coating, the desired immediate relief in patients suffering from nausea is obtained.

Karmoplex tablets are packed in bottles of 20, 60 and 250 tablets each.

DEXEDRINE PLUS

Dexedrine Plus' is intended for the treatment of overweight, especially in patients such as children and pregnant women, in whom the maintenance of an adequate supply of vitamins and minerals is essential. It presents, in a single capsule, a normal dose of 'Dexedrine' and an amount, adequate to satisfy nutritional requirements, of those essential vitamins and minerals that may be lacking from a low-calorie diet.

Dosage and Administration. The usual dosage of 'Dexedrine Plus' is 1 capsule 3 times a day, 30 to 60 minutes *before* meals. Some patients may need larger doses. With light sleepers, the last dose of the day should be given early enough to avoid interference with sleep.

Special Considerations. 'Dexedrine Plus' should be used with caution in patients hypersensitive to sympathomimetic compounds; in those cases of coronary or cardiovascular disease in which vasoconstrictors are contra-indicated; and in the presence of marked hypertension. Hyperexcitability and agitated prepsychotic states contra-indicate the use of the drug.

Formula. Each 'Dexedrine Plus' capsule contains:

Dextro-amphetamine sulphate ('Dexedrine')	5 mg.
Dicalcium phosphate, U.S.P.	250 mg.
Aneurine hydrochloride	0.4 mg.
Riboflavin	0.6 mg.
Nicotinamide	4 mg.
Ferr. Sulph. Exsic.	13.4 mg.
Vitamin A	1,680 Units
Vitamin D	500 Units

Packaging. 'Dexedrine Plus' is available in bottles of 50 capsules.

IMFERON (INTRAMUSCULAR IRON INJECTION)

Imferon is a solution of an iron-dextran complex which provides the equivalent of 50 mg. elemental iron in each millilitre.

Indications. Anaemia of pregnancy; impaired iron absorption; inadequate oral dosage; dietary deficiency; chronic blood loss; malnutrition; chronic infections; inflammatory conditions and cardiac diseases with low haemoglobin level.

Dosage. (*a*) Haemoglobin expressed as a percentage. The following formula gives the quantity of Imferon required to restore the haemoglobin concentration to normal when W = Patient's weight in pounds and Hb% = observed haemoglobin.

$$\frac{0.3\ W\ (100 - Hb\%)\ \text{ml.}}{50}$$

Example: A patient weighs 125 lb. and has a haemoglobin of 60%. The formula becomes

$$\frac{0.3 \times 125 \times (100 - 60)\ \text{ml.}}{50} = 30\ \text{ml.}$$

(*b*) Haemoglobin expressed as grammes per 100 ml. The formula is $\frac{1.3\ W\ (19 - Hb)\ \text{ml.}}{50}$

Example: A patient weighs 100 lb. and has a haemoglobin of 9.0 G./100 ml.

The formula becomes

$$\frac{1.3 \times 100 \times (19 - 9)\ \text{ml.}}{50} = 26\ \text{ml.}$$

For children the maximum doses are: over 20 lb. not more than 2 ml.; over 8 lb. not more than 1 ml.; under 8 lb. not more than 0.5 ml.

Administration. Imferon must be injected deeply into the upper outer quadrant of the buttock or the lateral aspect of the thigh. A 2-inch, 20 s.w.g. needle should be used.

Packing. 2 ml. ampoules containing the equivalent of 100 mg. of elemental iron are packed in 10's and 100's; 5 ml. ampoules containing the equivalent of 250 mg. of elemental iron are packed in 5's and 50's.

Distributors. Fisons Chemicals (S.A.) (Pty.) Ltd., 259 Commissioner Street, Johannesburg.

OXSORALEN AND VITILIGO

Oxsoralen (Elder) brand of methoxsalen is a compound (8-methoxypsoralen) isolated from plant sources for use in the treatment of vitiligo.

For many centuries inhabitants of Egypt, India and, to a lesser extent, other countries, attempted to treat vitiligo with extracts from certain plants. These substances (which aid in the production of melanin pigment) are found in several plants including *Fagara xanthoxyloides* and *Ammi majus* Linn.[1-4]

Formulation. Oxsoralen for *oral* therapy is obtainable in flesh-coloured capsules containing 10 mg. of 8-methoxypsoralen.

For *topical* treatment it is available in a clear acetone, alcohol, propylene glycol lotion containing 1% of 8-methoxypsoralen.

Indications. Oxsoralen is used orally, in combination (i.e. oral and topical) or topically, for the treatment of idiopathic vitiligo. Full details of the regimes of treatment can be obtained from the Distributors.

Contra-indications. Oxsoralen capsules should not be taken in the presence of liver insufficiency or diabetes mellitus.

Liver function tests should be done monthly for the first 3 months and then less frequently during course of treatment.

Oxsoralen has no effect on leucoderma associated with destruction of melanocytes which occurs following severe burns and trauma. It is not known to influence leucoderma consequent upon infections such as pinta or leprosy.

Distributors. Protea Pharmaceuticals Ltd., P.O. Box 7793, Johannesburg.

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1. El Mofty, A. M., (1948): J. Roy. Egypt. Med. Assoc., **31**, 651.
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3. Lerner, A. B., Denton, C. R. and Fitzpatrick, T. B. (1953): J. Invest. Derm., April.
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FLORINEF WITH GRANEODIN

OINTMENT OR LOTION FOR INFLAMMATORY AND ALLERGIC SKIN DISEASES

Description: *Florinef with Graneodin* combines the anti-inflammatory antipruritic action of Florinef (Squibb Fluorohydrocortisone Acetate) with the antibacterial action of Graneodin (Squibb Neomycin-Gramicidin).

The *Ointment* is 0.1% fluorohydrocortisone acetate combined with 2.5 mg. neomycin and 0.25 mg. gramicidin per gm. of plastibase (Squibb non-water-absorbing Oleaginous Ointment Base). The *Lotion* is 0.1% fluorohydrocortisone acetate combined with 2.5 mg. neomycin and 0.25 mg. gramicidin per ml. of an aqueous vehicle.

Action: *Florinef* is antipruritic and inhibits inflammatory reactions to bacterial, allergenic and other chemical agents. In many cases it is 25 times as potent as hydrocortisone.

Neomycin is effective *in vitro* against a variety of Gram-negative and Gram-positive organisms. Gramicidin is active *in vitro* against Gram-positive organisms, but has little effect on Gram-negative organisms. *Strep. haemolyticus*, resistant to neomycin, is highly susceptible to gramicidin. Organisms associated with most superficial infections of the skin are either destroyed or inhibited by neomycin-gramicidin.

Advantages: *Florinef with Graneodin* combines the potent anti-inflammatory, antipruritic therapy of fluorocortisone *plus* the prophylactic action of neomycin-gramicidin to guard against secondary infection.

It is effective in many patients who responded slightly or not at all to topical application of hydrocortisone.

Because of its broad anti-bacterial spectrum, *Graneodin* reduces the hazard of secondary invasion.

Sensitization to *Graneodin* is rare. If it does occur, topical *Graneodin* does not prevent subsequent use of oral or parenteral antibiotics.

XUM

Indications: *Florinef with Graneodin* is indicated in the treatment of non-infectious skin conditions known to respond to topical hydrocortisone or *Florinef* therapy. Dermatitis (atopic, eczematoid, contact—including poison ivy); dermatitis of the hands; neuro-dermatitis; lichen simplex chronicus; eczema (atopic, dyshidrotic, stasic, nummular); infant eczema; anogenital pruritus; sun burn. It is particularly useful against secondary infections.

Administration: *Florinef with Graneodin* should be applied sparingly and lightly over the affected area 2–4 times a day. Application to large areas does lead to percutaneous absorption.

Side Effects: Sodium retention with oedema has been reported in rare instances after fluorocortisone. If oedema occurs, discontinue the drug temporarily. Potassium chloride 3 gm. per day and restriction of dietary sodium may speed disappearance of oedema.

Packaging: *Ointment*, 5 gm. collapsible tubes; *Lotion*, 15 c.c. plastic squeeze bottles.

Distributors: Protea Pharmaceuticals Ltd., P.O. Box 7793, Johannesburg.

MYCOSTATIN (SQUIBB MYSTATIN)

Description: Mycostatin (derived from cultures of *Streptomyces noursei*) is recommended for prevention and treatment of intestinal moniliasis associated with oral administration of antibiotics.

Physical Properties: Crystalline Mycostatin is a pale yellow, almost colourless substance, empirical formula $C_{46}H_{73}NO_{18}$, considerably less soluble than impure material, relatively stable when dry but breaking down rapidly in the presence of water.

Antifungal Activity, in vitro: It inhibits or kills all species of fungi and yeasts tested, except for Actinomycetes. Its greatest effect is on yeast-like fungi in the growing stage; less active against spores and inactive against bacteria.

Absorption and Excretion: Mycostatin is poorly absorbed *per os;* negligible amounts appear in the blood, but considerable amounts in the stool.

Toxicity: Virtually non-toxic *per os*. Patients have tolerated oral doses up to 6 million units daily for several months without systemic toxicity or sensitization, although the larger doses caused nausea, vomiting or diarrhoea in a few cases. It was not always possible to distinguish side effects of Mycostatin from those of chlortetracycline given concurrently. In one report, 5.4 million units daily caused no side effects; but vomiting occurred with twice that amount.

Indications: The tablets are indicated for the suppression of intestinal fungi and yeasts, particularly in patients under protracted oral treatment with antibiotics active against intestinal bacteria.

Patients prepared for intestinal surgery with oral antibiotics should also be protected by Mycostatin.

It is recommended for treatment of patients with evidence of intercurrent infection with intestinal fungi.

A considerable number of patients on oral antibiotics, without the full-blown picture of clinical moniliasis, have intestinal inflammation and diarrhoea, sometimes with ulceration and anal fissure. Intestinal moniliasis may be a prelude to generalized infection. Such developments can be prevented by Mycostatin; established monilial infection of the intestine can be cleared up by the drug in 24-48 hours.

Dosage: One 500,000-unit tablet 3 times daily, by mouth. If fungi are not adequately suppressed, the dose may be doubled. Mycostatin may be given in conjunction with all commonly used oral antibiotics and should be continued at least as long as the antibacterial agent. It may advantageously be continued for a short time longer.

Packaging: 500,000-unit tablets, bottles of 12 and 100.

Distributors: Protea Pharmaceuticals Ltd., P.O. Box 7793, Johannesburg.

PENTOXYLON

Pentoxylon represents a new approach to the total problem of angina pectoris, i.e. it is aimed at relieving coronary spasm *and* the apprehension of the patient living in dread of the next attack. This has appropriately been termed 'therapy in depth' and has as its goals the reduction of nitroglycerin requirements, the prevention or alleviation of anginal attacks, and the abatement of the psychic stress resulting from fear and constant apprehension.

Each long-acting tablet contains 10 mg. of pentaerythritol tetranitrate and 1 mg. of Rauwiloid.

Clinical trials have shown that Pentoxylon is well tolerated; side actions were mild and uncommon. Even headache did not occur in more than 10% of cases and was readily relieved by aspirin without withdrawal of the drug. Tolerance does not develop.

The full effectiveness of Pentoxylon requires more than 2 weeks of therapy to develop, though marked benefits are usually perceived after 24 to 48 hours.

The usual dosage is one tablet q.i.d., but doubling of this amount is sometimes desirable and will be well tolerated.

The only possible contra-indication is glaucoma, but recent work makes even this doubtful.

Pentoxylon is available through the usual channels in containers of 25 and 100 tablets. It is manufactured by Riker Laboratories Africa (Pty.) Ltd., P.O. Box 1355, Port Elizabeth, who will gladly send literature and clinical trial material on request.

ORAL BICILLIN

Wyethical (Pty.) Ltd. announce the introduction of a new variant of oral Bicillin (Benzathine Penicillin G) in the form of paediatric drops, ideal in the treatment of the common infections of infancy caused by penicillin-sensitive organisms.

This new dosage form of Bicillin is so highly concentrated and delightfully flavoured that it can be given to infants without conditioning them to reject their formula or other feeding, as often happens when antibiotics are administered in the food. Moreover, mothers need not worry about getting every dose of medicine into the child by way of feeding, because Bicillin drops, like other oral forms of Bicillin, offer surety of resistance to gastric degradation. Bicillin Drops, therefore, can be given before, after or with nourishment.

Each c.c. of this stable and palatable suspension provides 150,000 units of Bicillin. The dropper is calibrated to deliver 100,000 units—a convenient paediatric dosage strength.

Packed in bottles of 10 c.c.

XUM

XUM

New

IRON BY INTRAMUSCULAR INJECTION

BENGER LABORATORIES, who introduced the first intravenous iron preparation, now present a new and equally effective iron complex for intramuscular administration. ITS NAME IS IMFERON. The introduction of this new compound considerably simplifies the control of iron deficiency anaemias in both hospital and general practice.

Note these advantages . . .

★ **Imferon** is the first effective preparation of iron to be suitable for intramuscular administration.

★ **Imferon** provides the rapid, reliable response of an order hitherto only obtainable with intravenous preparations; and it is much less time-consuming to administer.

★ **Imferon** is particularly indicated for the patient who is refractory to, or intolerant of, oral iron; and when a rapid response is required, as in anaemia of pregnancy.

★ **Imferon** provides the equivalent of 50 mg. of iron in each millilitre.

AMPOULES 2 ml. (100 *mg. Fe.*) boxes 10 and 100.
AMPOULES 5 ml. (250 *mg. Fe.*) boxes 5 and 50.
Fully-descriptive literature on request.

Imferon TRADE MARK

Iron-Dextran Complex

A PRODUCT OF

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RESEARCH

Further information from

FISONS CHEMICALS

(S.A.) (Pty.) Ltd.
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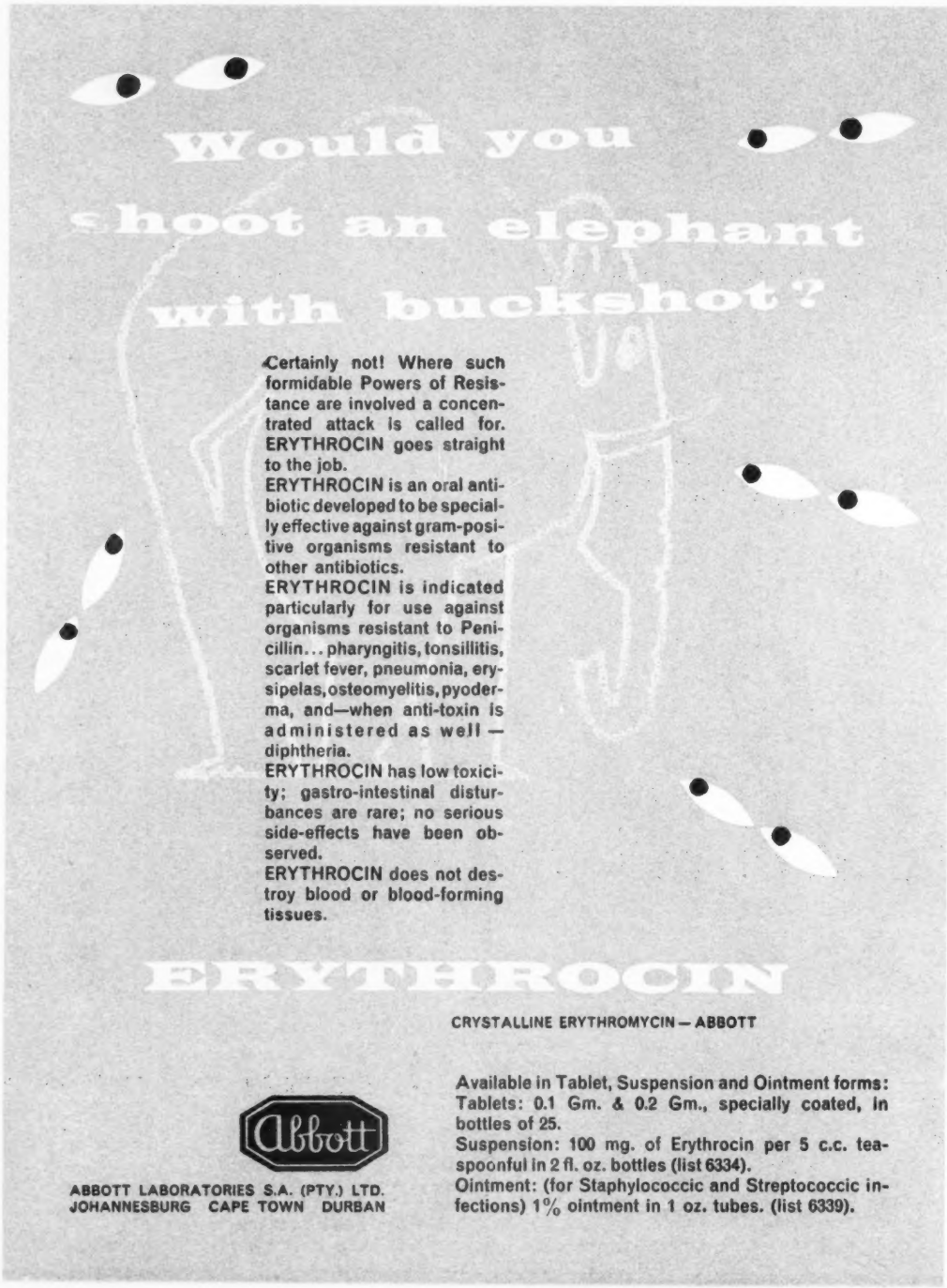
259, Commissioner Street. P.O. Box 5788, Johannesburg.

XUM


Would you
shoot an elephant
with buckshot?
Certainly not! Where such formidable Powers of Resistance are involved a concentrated attack is called for. ERYTHROCIN goes straight to the job.
ERYTHROCIN is an oral antibiotic developed to be specially effective against gram-positive organisms resistant to other antibiotics.
ERYTHROCIN is indicated particularly for use against organisms resistant to Penicillin... pharyngitis, tonsillitis, scarlet fever, pneumonia, erysipelas, osteomyelitis, pyoderma, and—when anti-toxin is administered as well — diphtheria.
ERYTHROCIN has low toxicity; gastro-intestinal disturbances are rare; no serious side-effects have been observed.
ERYTHROCIN does not destroy blood or blood-forming tissues.
ERYTHROCIN
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ABBOTT LABORATORIES S.A. (PTY.) LTD.
JOHANNESBURG CAPE TOWN DURBAN
Available in Tablet, Suspension and Ointment forms:
Tablets: 0.1 Gm. & 0.2 Gm., specially coated, in bottles of 25.
Suspension: 100 mg. of Erythrocin per 5 c.c. teaspoonful in 2 fl. oz. bottles (list 6334).
Ointment: (for Staphylococcic and Streptococcic infections) 1% ointment in 1 oz. tubes. (list 6339).

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